ONE SIZE DOES NOT FIT ALL

Wim PINXTEN

ACTA BIOMEDICA LOVANIENSIA

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ONE SIZE DOES NOT FIT ALL
INTEGRATING ETHICAL AND LEGAL GUIDANCE INTO PEDIATRIC CLINICAL RESEARCH

LEUVEN UNIVERSITY PRESS

Acknowledgements

A PhD is an intensive, exciting, and most of all fun journey. I have experienced the opportunity to dedicate four years of my professional life to this project as a most generous gift, for which I am deeply grateful. I am equally grateful for the many encounters along this journey, all contributing in a unique and essential way to the course that I have taken and the results that we have jointly realized. I was very privileged to meet so many excellent and experienced guides on my way, and it is with great joy that I take the opportunity to address a personal word of gratitude to the most notable among them.

Prof. dr. Kris Dierickx, prof. dr. Herman Nys, and prof. dr. Chris Van Geet, the promotores of this thesis, provided me with excellent intellectual and material working conditions. They always took ample time to discuss the design, progress, and results of my research. I thank them for their trust and support, for their patience and their criticism, and for granting me access to their expertise in the domain of medical ethics, health law, and clinical practice.

Prof. dr. Geertrui Van Overwalle and prof. dr. Martin Hiele, members of the thesis advisory committee, I thank for the support, criticism, and constructive advice they provided from their background in clinical practice, ethics committees, and (patent) law when we discussed the formal progress reports of this project.

I am very grateful to prof. dr. M. Hiele, prof. dr. M. Kruger, prof. dr. G. Van Overwalle, prof. dr. T. Roskams and dr. F. Thiele for having accepted to act as members of the doctoral examination board, for reading the manuscript and for the constructive criticism.

Essential parts of this dissertation were either inspired by or based directly on the results of fieldwork. I owe immense gratitude to the clinicians and other healthcare professionals who granted me access to their daily practice (for reasons of confidentiality, I will not mention their names). Their dedicated cooperation to this project enabled me to access original and inspiring data, which nourished the analysis of ethical, legal, and social issues in pediatric clinical research in this dissertation abundantly.

Grateful acknowledgement is also made to the European Commission, for the partial financial support of this project.

My former colleagues at the Centre for Biomedical Ethics and Law, who all contribute to the inspiring and warm working environment of the centre, I owe gratitude for their support, collegiality and friendship. I am equally grateful to all those who encouraged and supported the continuation of my scientific activities. In this respect, I am particularly indebted to my colleagues of the Department of Medical Ethics and Philosophy of Medicine of the ErasmusMC Rotterdam and to my colleagues of the Department of Healthcare and Technology of the KHLeuven, for providing a challenging and stimulating environment to nurture, broaden, and validate the expertise that I have generated in this project.

The contribution of family and friends to a PhD is probably the most difficult to describe, though not the least important. I am particularly grateful to my parents, who have always encouraged and supported my education. Unfortunately, in 2008, my family lost her mother, whose human excellence will always remain inspiring and exemplary. I cannot possibly describe in words what I am indebted to her. No less, I am indebted to my father, who has always been committed to my life and future as no one but a parent can. Dear family and friends, thank you for being there!

Lisa, to you I address a special word of gratitude. My joy in employment and life have always been of major concern to you, and you are the one who always realized that research was the right course for me to take. Always vigilant to prevent that family life and professional activity would grow incompatible, you committed to create the time and space I needed to make this journey, and to continue it in an open future. I have considered dedicating this dissertation to you, when I realized that there is so much else in life to dedicate. The best will always be yours!

Dankuwel

Wim Pinxten

January 2011

List of Abbreviations

EMA or EMEA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference for Harmonization
IMP	Investigational medicinal product
LEH	Law of 7 May 2004 concerning experiments on the human person
PDCO	Pediatric Committee
PIP	Pediatric Investigation Plan
PUMA	Pediatric Use Marketing Authorization
RCT	Randomized Controlled Trial
REC	Research Ethics Committee

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General Introduction

Research rationale

Background

In the course of the twentieth century, the ethical and regulatory stance towards medical experiments involving children has changed dramatically.[1] Where initially the successes of medical science had created a strong trust in the biomedical enterprise, the scandalous research events that occurred during the Second World War and in its aftermath raised considerable suspicion about the ethical acceptability of clinical research. In particular, the discussion on the acceptability of conducting clinical research in vulnerable children has provoked harsh controversy,[2-4] since diverging standpoints have been defended by prominent ethicists.[5]

The predicament

While medical ethicists quested for an appropriate ethical stance towards pediatric clinical research, an overall reluctance to involve minors in clinical research rendered innovations in the field of pediatric drug development scarce. As a result, a stringent lack of licensed drugs that are labeled for pediatric use is tangible in pediatric practice to date, resulting in a high rate of off-label prescriptions.[6-9] This predicament, however, cannot just be attributed to a lack of consensus in the field of medical ethics. Quite the reverse, diverse and complex causes, many of which are far removed from the work of bioethicists, render pediatric clinical research a precarious enterprise. These causes can be related to individual persons, and the pediatric population at large.

At the *personal level*, significant differences between minors and adults exist. Physically, minors are not small adults because of major differences in the composition and functioning of the body. This renders it impossible to extrapolate research data that have been obtained in competent adults to the population of minors in a reliable way (e.g., by dose recalculation based on body weight or skin surface).[10 11] Also psychologically, many differences between minors and adults exist, for example with regard to understanding and maturity. At the *population level*, at least four factors make that pediatric clinical research requires a specific approach of scientific, ethical, legal, social, and economical issues. First, the population of minors is relatively small and very heterogeneous,[12] which may complicate the recruitment of an adequate number of eligible research subjects.[13 14] In addition, the small population indicates a small market, rendering the return on investment of pediatric clinical trials uncertain under the regular market conditions.[15] Second, a number of diseases only occur in minors, or prompt for diagnosis, prevention or treatment in early childhood (e.g., in the case of chronic diseases the pathology of which increases over time). In addition, children may be in need of specific administration forms, different from those available to adults (e.g., liquid solution in stead of tablets). Third, pediatric clinical trials require specific research designs,

including specific normal values and specific endpoints. Fourth, unique ethical, legal, and social issues arise when minors are enrolled in clinical studies. In this respect, the vulnerability of minors as a population has been emphasized strongly, and the ethical acceptability of enrolling minors in clinical studies has been debated fiercely.

Because of the differences between minors and adults, both as *persons* and as *populations*, there exists an unequivocal need to conduct clinical research in the population of minors. Although Harry Shirkey reported already in 1968 that in absence of pediatric clinical research minors would be turned into 'therapeutic orphans',[16] pediatric patients have been ignored in clinical research for long and systematic efforts to encourage the inclusion of minors in clinical studies only came decades later.[17 18] Today, the urgent need for pediatric clinical research in the population of minors continues to exist, even though it has been generally recognized that pediatric clinical trials are indispensible to provide minors with a gamut of safe and efficacious drugs that is equitable to that available to their adult counterparts. In addition, the important differences between adults and minors make that paradigms of clinical research, research ethics and research regulation that are grafted on the competent adult do not adequately respond to the specifics of pediatric clinical research. Therefore, specific attention must be paid to the ethical, legal, and social issues in pediatric clinical research. In other words: one size does not fit all.

State of the art

Medical Ethics

Ethical refection frequently tends to focus on a canonical list of ethical issues that are discussed in depth in literature. These discussions range from the exploration of conceptual and semantic niceties to empirical-ethical studies. Also with regard to the ethical, legal, and social issues in pediatric research, a canonical list of ethical issues can easily be drafted. Among others, such a list would definitely include the issues of (1) informed consent, assent, and dissent,[19-25] (2) the protection of vulnerable research subjects,[1] (3) risk thresholds,[26-29] and the (4) the payment of research subjects.[30-32]

Notwithstanding the validity of canonical issues in pediatric research conduct, various unique and important issues in pediatric clinical research exceed the traditional canonical lists of ethical issues and have not or only insufficiently been addressed in literature thus far. Other issues have been addressed extensively, but remain in search of an adequate and realistic approach.

Health Law

In the course of the past two decades, important efforts have been made to encourage the conduct of clinical research in minors. In the European Union, the establishment of a harmonized legal framework to regulate the conduct of clinical research across the borders of individual member states has been a milestone in this process.[18 33-38] The regulation that currently governs pediatric clinical research, however, covers several legal systems and no

less than 22 languages, which renders this legal framework difficult to access and understand. In addition, diverse regulations, which have been issued by multiple legislative bodies, coexist within the European legal landscape. As a result, the European legal framework hosts a considerable diversity in its provisions, the clarity and consistency of which have not been investigated properly to date.

Good clinical practice in pediatric research conduct

Pediatric clinical research must comply with ethical and regulatory requirements. However, the ethical and regulatory frameworks that govern pediatric clinical research in the EU are not ready to use instruments that can be implemented effortlessly into pediatric research practice. Quite the reverse, it is to be expected that the applicable ethical and legal requirements will sometimes prove hard to implement in clinical practice, given the need for extensive interpretation and the potential for unclear or contradictory provisions.

To date, little is known about how ethical and regulatory requirements for the conduct of pediatric clinical research are actually implemented into practice in EU member states. In addition, it is not clear to what extent the current ethical and regulatory frameworks respond to the major ethical issues that medical practitioners experience when they conduct clinical research in the population of minors.

Objectives

Four research objectives are central to this dissertation: (1) the improvement of the access to and insight in the European legal frameworks that govern pediatric clinical research; (2) the comparative analysis of relevant regulation at the supranational level and at the national level; (3) the enquiry of the operational implementation of legal good clinical practice requirements in informed consent discussions; and (4) the ethical analysis of specific issues in pediatric clinical research.

Improving the access to and insight in the European legal frameworks that govern pediatric clinical research

Map the regulation governing pediatric clinical research in the EU, both at the supranational level and at the level of individual EU Member States. List, analyze, and address contingencies, inconsistencies, and contradictory provisions in the European legal framework.

Comparative analysis of relevant regulation

Comparative analysis of the regulation governing pediatric clinical research at the supranational level and at the level of individual EU member states. Identification and analysis of unclear elements, inconsistencies, and contradictory provisions.

Enquiry of the operational implementation of ethical and legal requirements in informed consent discussions in clinical research

Explore and discuss the operational implementation of ethical and legal requirements in pediatric clinical research. Discuss the adequacy of existing ethical and regulatory frameworks to address the ethical issues that minors, their parents, and clinicians encounter when minors are enrolled in clinical studies.

Ethical analysis of specific issues in pediatric clinical research

Identify and analyze specific ethical issues in the conduct of pediatric research. Compound an inventory of key ethical issues that are either novel or in continuing search for consensus. Analyze a limited number of ethical issues in depth, including: (1) non-clinical objectives in clinical research, (2) the regulation of trust, (3) patients' access to investigational medicinal products, and (4) the fair allocation of resources to the prevention, diagnosis, and treatment of rare diseases.

Scope and methodology

Bioethics is a relatively recent phenomenon that remains in search of a clear identity to date. As a result, various views on the prospect, nature, and methodologies of bioethics coexist.[39] This indicates an ontological and conceptual heterogeneity, that becomes apparent in the many parallel approaches that coexist in contemporary bioethics, each claiming their own validity (e.g., utilitarianism, rights based approach, empirical ethics).[40] While such parallel validity claims often generate exclusive and competing stances toward particular ethical issues, the inherent ontological and conceptual heterogeneity of bioethics can be approached differently. In this dissertation, efforts have been made to integrate diverse theories of medical ethics, methodological approaches and heterogeneous data by assembling three complementary tracks of ethical enquiry: contextual analysis, normative qualification, and practical guidance. Contextual analysis drafts the state of the art of ethical, legal, and social issues in pediatric clinical research, both in theory and in practice. Normative qualification delineates the normative targets for ethical research conduct and healthcare provision. Practical guidance aims at integrating ethical and legal guidance towards the normatively qualified targets in the actual practice of pediatric clinical research. Expressed commonsensical, these three tracks of enquiry address three questions that are essential for the successful and responsible realization of any human enterprise, respectively: *(1) where do we stand, (2) where are we heading for, and (3) how can we get there?*

Contextual analysis

Ethical, legal, and social issues do not occur in a contextual void. They are shaped within the specific social setting in which they occur, and by consequence ignoring the social context of ethical and regulatory issues comes at the risk of short-sighted reflection, practical irrelevance or even the elucidation of merely fictive problems. To reduce these

risks, it is essential that ethical, legal, and social issues in pediatric clinical research be analyzed against the background of the social context in which they occur. In this respect, contextual analysis aims at drafting the state of the art of ethical, legal, and social issues in pediatric clinical research and the way in which these issues are addressed in medical ethics, health law, and public policy. As such, contextual analysis is essential to provide an answer to various questions that are highly relevant to our enquiry, for example:

- What ethical, legal, and social issues are deemed specific to pediatric clinical research? What problems do these issues cause to practitioners, minors, and their parents? What efforts are made to respond to these problems?
- Which regulation governs pediatric clinical research conduct? To what extent is this regulation harmonized? What unclear provisions, inconsistencies, and contradictory requirements exist in law? What contradictory stances coexist in medical ethics? What ethical and regulatory issues need to be addressed?
- How do medical practitioners, minors, and their parents deal with ethical, legal, and social issues? How do they interpret and implement the ethical and legal requirements? Are the ethical, legal, and social issues that they experience addressed in ethics and law?

Normative qualification

Addressing ethical, legal, and social issues in pediatric clinical research is not merely a matter of technique, but also a precarious exercise to provide normative orientation. Such orientation can be provided in two ways. First, it can be aspired to prevent, avoid, and condemn what is considered to be unethical. Myriad historical examples illustrate this process, since many major ethical and legal regulations have been issued in response to research scandals.[2] Second, it can be aspired to pursue what is considered to be ethical. Here, the *good* that is aspired needs not to be an invariable and irrefutable entity. This is clearly illustrated by the concept of *good clinical practice*, a set of requirements that is generally accepted, though open to evolution and change (as the many revisions of the Declaration of Helsinki illustrate).[41] In addition, it must be acknowledged that several concepts of the good coexist: *individual* concepts of the good (such as personal values), and *social* concepts of the good (such as norms and regulations).

Different types of normative reflection provide normative qualification to the objectives that are aspired in human enterprises, each having specific assets and demerits.[42] For example, academic theoretical reflection is an excellent way to dismantle unsound reasoning, but has been extensively criticized for its limited practical problem-solving capacities. Indeed, dealing with ethical issues at a theoretical level by no means guarantees an adequate approach of these issues in practice. Alternately, clinical ethics may be praised for its capacity to adequately address ethical issues on a case-by-case basis, but can been criticized for its normative impurity. Necessarily, a case-by-case approach will lack the general validity that is characteristic to theoretical normative reflection. In turn, empirical ethics opens up new potential to design more realistic approaches to ethical issues, and

enables to identify ethical issues that traditionally do no receive any attention. However, the way in which empirical data and normative reflection are to relate remains a source of controversy to date,[43] and empirical data do not demonstrate what is ethical in itself.

With regard to pediatric clinical research, normative qualification is essential to provide an answer to various questions that are highly relevant to our enquiry, for example:

- What research do children need?
- What legitimate claim to safe and efficacious drugs do children have?
- What research is deemed unethical in children?
- What pursuit of health is considered to be ethical?
- What is society's duty towards children?
- What are the implications of the vulnerability of children?
- What constitutes "Good Clinical Practice"?
- How do personal values, ethical norms and legal rules relate? What is their role and righteous place in medical decision-making?

Practical guidance

The combination of a sound awareness of the social context in which ethical, legal and social issues are shaped and the clear normative qualification of the endpoints we pursue in our reasoning and action does not constitute, support, or direct ethical conduct in itself. In other words, knowing where we stand and where we are heading for, does not discharge us from navigating through a complex landscape, seeking orientation and surpassing obstacles along the road.

Throughout the recent history of medical ethics and health law, ethical principles (e.g., the four major principles of biomedical ethics[44]) have played a key role in the search for practical guidance. Although it must be emphasized that ethical principles are not an end in itself but a means to another normative end, principles do enable to graft reasoning and action to normatively qualified endpoints. Nonetheless, ethical principles have also been harshly criticized for their limited practical problem solving capacity.[45] Against this background, alternate ways to provide normative guidance have been explored and remain in need of further exploration.

With regard to pediatric clinical research, practical guidance is essential to provide an answer to various questions that are highly relevant to our enquiry, for example:

- Which normative orientation is provided to pediatric clinical research?
- How can efficacious operational guidance be integrated into pediatric clinical research?
- How can we deal with conflicting values, norms, and rules in practice?

Multidisciplinary approach

In this dissertation, we have integrated three types of data and three methods of analysis in a single, multidisciplinary approach, using a newly designed conceptual framework (cf. chapter 1), covering (1) literature review, (2) comparative law study, and (3) qualitative empirical research.

The literature study covers scientific literature with regard to the general ethical concerns and the specific ethical issues that are analyzed in this dissertation.

The comparative law study comprises the supranational and national regulation that governs pediatric clinical research across the borders of individual EU member states. In addition, the Belgian regulatory framework has been analyzed in greater detail.

For the qualitative empirical analysis, empirical data have been generated through observational research. By its design, the observational study covers different age subgroups in pediatrics and comprises both patients and a limited number of healthy volunteers. Diverse types of pediatric wards, clinical trials, and diseases are covered in the analysis.

Research results: Outline of the doctoral dissertation

Chapter 1: Supranational regulation in the EU

Pinxten, W., Dierickx, K., Nys, H. (2009). Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. European Journal of Pediatrics, 168(10), 1225-1234.

Abstract: In this chapter, the European legal framework surrounding pediatric clinical trials is analyzed from the perspective of the major ethical concerns in pediatric research. The four principles of biomedical ethics will be used as a conceptual framework (1) to map the ethical issues addressed in the European legal framework, (2) to study how these issues are commonly handled in competent adults, (3) to detect workability problems of these paradigmatic approaches in the specific setting of pediatric research, and (4) to illustrate the strong urge to differentiate, specify, or adjust these paradigmatic approaches to guarantee their successful operation in pediatric research. In addition, a concise comparative analysis of the European regulation is made. To conclude the analysis, the findings are integrated in the existing ethical discussions on issues specific to pediatric clinical research.

Chapter 2: Domestic regulation in individual EU Member States

Pinxten, W., Dierickx, K., Nys, H. (2010) Diversified Harmony, Supranational and domestic regulation of pediatric clinical trials in the European Union. Journal of Cystic Fibrosis [Accepted].

Abstract: In this chapter, the regulation that currently governs pediatric clinical research conduct at the supranational level of the EU and at the level of individual EU member states is analyzed. The analysis focuses on the way in which the national and supranational legal

frameworks address five ethical issues that are specific to pediatric clinical research: (a) informed consent, (b) the necessity to conduct research in minor subjects, (c) the interests of the subject concerned, (d) the risks and burdens involved, and (e) the pediatric expertise of protocol review committees. The chapter is concluded with a discussion of the harmonization and diversification of the legal requirements that govern pediatric clinical research in the EU.

Chapter 3: The Belgian law

Pinxten, W., Dierickx, K., Nys, H. (2008). The implementation of Directive 2001/20/EC into Belgian law and the specific provisions on pediatric research. European Journal of Health Law, 15(2), 153-61.

Abstract: This chapter provides an overview of the requirements for involving minors in medical experiments that are captured in the Law of 7 May 2004 concerning experiments on the human person (LEH), and analyzes the dissimilarities between the LEH and the European Directive.

Chapter 4: Beyond regulation

Pinxten, W., Nys, H., Dierickx, K. (2008). Regulating trust in pediatric clinical trials. Medicine, health care, and philosophy, 11(4), 439-444.

Abstract: In this chapter, it is analyzed how the enrollment of minors in clinical trials is negotiated within relationships of mutual trust between clinicians, minors, and their parents. After a brief description of the problems associated with involving minors in clinical research, it is considered how existing ‘‘relationships of trust’’ can be used as a place where the concerns of research subjects can be more fully discussed and addressed. Building on the tacit recognition of trust found in The European Clinical Trials Directive, policy recommendations are made to allow for clearer, more ethically informed guidelines for enrolling minors in clinical research.

Chapter 5: Essentials for the ethical and regulatory agenda

Pinxten, W., Nys, H., Dierickx, K. (2010). Frontline ethical issues in pediatric clinical research. Ethical and regulatory aspects of seven current bottlenecks in pediatric clinical research. European Journal of Pedatrics 169(12),1541-8.

Abstract: This chapter explores seven bottlenecks in the ethical guidance and legal regulation that currently governs govern pediatric clinical research: (1) the integration of research in therapy, (2) the education of clinicians, (3) the empowerment of families, (4) the harmonization of protocol review, (5) the assessment non-clinical research objectives, (6) the control of placebo use, and (7) the provision of fair incentives for pediatric research conduct. For all of these issues, a clear view on the way forward is largely lacking, either because these issues have not been discussed in depth to date, date or because the existing debates have failed to generate a generally supported consensus.

Chapter 6: Current controversies in search of normative orientation: access to investigational medicinal products for minors

Pinxten, W., Nys, H., Dierickx, K. (2010). Access to investigational medicinal products for minors. Ethical and regulatory issues in negotiating children's access to investigational medicines. Journal of Medical Ethics 36: 791-794.

Abstract: The quest for access to investigational drugs is particularly relevant to pediatric practice, where a significant share of the drugs prescribed has never been tested in children or labeled for use in the pediatric population. In this chapter, the ethical concerns in two potential tracks of seeking access to investigational medicinal products (IMP) for minors are explored: access on an individual basis, and collective access, via patient organizations. In the discourse, several unique ethical and regulatory concerns related to the direct negotiation of access to IMP for minor patients are identified, with a focus on product safety, the recruitment of research subjects, the unnoticed entry of market mechanisms in the recruitment of research subjects, and the sidelining of third parties in the recruitment process. The chapter is concluded with a concise reflection on the way forward.

Chapter 7: Current controversies in search of normative orientation: non-clinical research objectives

Pinxten, W., Nys, H., Dierickx, K. (2009). Ethical and regulatory issues in pediatric research supporting the non-clinical application of fMR imaging. American Journal of Bioethics, 9(1), 21-23.

Abstract: Over the past decades, important efforts have been made to regulate the involvement of children in clinical trials. However, current ethical and legal procedures surrounding clinical trials in minors (US/EU) are not designed to consider and assess the non-clinical use of medical technologies such as fMRI, while non-clinical applications of pediatric fMRI cannot be developed without conducting clinical trials in children. In this chapter, the diverse ethical issues related to the non-clinical applications of fMRI are discussed from the perspective of pediatric clinical trial regulation

Chapter 8: Current controversies in search of normative orientation: distributive justice: funding the development and supply of orphan drugs

Pinxten, W., Denier Y., Dooms M., Dierickx, K. (2010). A fair share for the orphans. Justice, rationality and arbitrariness in the allocation of limited healthcare resources to the prevention and treatment of rare diseases. [Unpublished manuscript]

Abstract: For a significant number of patients, no or only poor interest in developing a treatment for their disease or condition exists. Especially with regard to rare conditions, the lack of commercial interest in drug development is a burning issue. This is particularly relevant to pediatrics, where rare diseases have a relatively high prevalence.

To address the commercial disinterest in these conditions, several interventions have been made in the regulatory field. However, existing regulations mainly focus on the provision of incentives to the sponsors of clinical trials of orphan drugs, and leave the

overarching question on the righteous place of orphan drugs in resource allocation systems unanswered.

In this chapter, major ethical issues in the development and supply of treatments for rare conditions are analyzed. Subsequently, an ethical framework, which can help health policy makers in moving forward in the difficult issue of justly allocating resources to the prevention and treatment of rare diseases is presented.

Chapter 9: Empirical exploration of the implementation of ethical and legal guidance in pediatric clinical research

Pinxten, W., Nys, H., Dierickx, K., Van Geet, C. (2010). The implementation of the European Good Clinical Practice Directive in informed consent discussions [Submitted for review].

Abstract: **Objectives:** In this chapter, practical issues in implementing ethical and legal requirements in pediatric research practice are empirically explored. The findings that are presented serve as a first illustration of how empirical enquiry can be integrated in the analysis of ethical, legal, and social aspects of pediatric clinical research, using the conceptual framework that has been developed in this doctoral thesis (cf. chapter 1). In addition, the findings that are presented in this chapter aim at informing the normative discussion of major tensions in pediatric research practice empirically (cf. general discussion). The analysis in this chapter focuses on the implementation of the national and supranational legal frameworks governing pediatric clinical research in informed consent discussions.

Methods: Practical issues in the operational implementation of ethical and legal requirements in pediatric research practice are empirically explored by means of an observational study of 23 informed consent discussions. Recognizing that the European legal framework imposes a single set of legal requirements to a large diversity of pediatric clinical trials, consent discussions were observed for a large variety of studies, diseases, sponsors, and study designs. The discussions were audio taped, transcribed, coded and analyzed qualitatively, linking the content of the informed consent discussions to three major concerns in the European legal framework. Only oral communication was taken account, even though additional written information was provided to the parents and/or minor subjects.

Against the background of the modest objectives of this empirical exploration, the limited sample size, the explicit choice to study pediatric clinical research in its full heterogeneity, and concerns to protect the anonymity of the clinicians, minors, and their parents involved, some types of analysis have been abandoned. In this respect, no links between observations and specific studies have been made, and no counts of the number of cases in which particular observations were present are given, since this type of analysis is likely to create a deceptive view given the small and heterogeneous sample of cases.

It is fully acknowledged that the analysis does not generate any generalizable knowledge, and that the findings presented in this chapter could not be saturated in within the limits of

this empirical exploration. Nonetheless, the findings in this chapter suggest a number of issues that are highly relevant to analyze and discuss the operational implementation of ethical and legal requirements in pediatric research practice. As such, this analysis serves as a first inventory of practical issues that can inform (1) pragmatic decision-making and (2) the design of further, more comprehensive clinical research.

Results: From the observed consent discussions, there are few indications that European legal good clinical practice (GCP) requirements are systematically implemented. We found no indications that the European legal framework offers strong impetuses for the realization of legal GCP-requirements at the interpersonal level of addressing ethical issues.

In addition, our analysis sheds a new light on five important ethical tensions: (1) harmonization versus heterogeneity (2) informed consent versus documented consent, (3) assent versus procedure compliance, (4) direct benefit versus valid research results, and (5) risk-benefit ratio versus risk-risk ratio.

Conclusion: It is both relevant and important to define and support the tasks, roles, and interests of minors, parents, and researchers in the informed consent process. Our observations draft a background against which these tasks, roles, and interests can be explored.

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Part I

Navigating through the regulatory landscape

Chapter 1: Supranational regulation in the EU

Pinxten, W., Dierickx, K., Nys, H. (2009). Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. European Journal of Pediatrics, 168(10), 1225-1234.

Abstract

The involvement of minors in clinical research is inevitable to catch up with the lack of drugs labeled for pediatric use. To encourage the responsible conduct of pediatric clinical trials in the EU, an extensive legal framework has been developed over the past decade in which the practical, ethical, legal, social, and commercial issues in pediatric research are addressed. In this article, the European legal framework surrounding pediatric clinical trials is analyzed from the perspective of the major ethical concerns in pediatric research. The four principles of biomedical ethics will be used as a conceptual framework (1) to map the ethical issues addressed in the European legal framework, (2) to study how these issues are commonly handled in competent adults, (3) to detect workability problems of these paradigmatic approaches in the specific setting of pediatric research, and (4) to illustrate the strong urge to differentiate, specify, or adjust these paradigmatic approaches to guarantee their successful operation in pediatric research. In addition, a concise comparative analysis of the European regulation will be made. To conclude our analysis, we integrate our findings in the existing ethical discussions on issues specific to pediatric clinical research.

Introduction

The safety and efficacy of a large number of the drugs used in pediatric practice has not been demonstrated for the specific use in children.[1] Because children are not simply small adults, results of clinical trials in adults cannot often be reliably extrapolated to minors.[2] Therefore, there is an urgent need to perform clinical trials on children.

At present, it is widely recognized that it is not possible to provide children with a variety of safe and efficacious drugs comparable to those available to adults without involving minors in clinical trials. To catch up with the lack of licensed drugs that are labeled for pediatric use, regulatory efforts have focused on facilitating, encouraging, and rewarding the conduct of clinical research in minors. Nonetheless, the development of safe and efficacious drugs for use in children remains a precarious enterprise.[3] Several constraints work against the marketing of drugs tested in children and labeled for pediatric use, among which practical difficulties (e.g., recruitment issues)[4 5], strict ethical and legal requirements (e.g., restrictive policy concerning non-beneficial research, cf. infra), and economic issues (e.g., the limited potential for return on investment in pediatric trials).[6] In the EU, this predicament is addressed in an extensive legal framework that has been developed over the past decade.

In this article, the European legal framework surrounding pediatric trials is analyzed from the perspective of the major ethical concerns in pediatric research. First, the content and implementation of the European legal framework will be presented and clarified using the four principles of biomedical ethics.[7] The well-known principles of justice, non-maleficence, beneficence, and autonomy will be used as a starting point (1) to map the ethical issues addressed in the European legal framework, (2) to study how these issues are commonly handled in competent adults, (3) to detect workability problems of these paradigmatic approaches in the specific setting of pediatric research, and (4) to illustrate the strong urge to differentiate, specify, or adjust these paradigmatic approaches to guarantee their successful operation in pediatric research. Second, a concise comparative analysis of the European regulation will be made. To conclude our analysis, we will integrate our findings with the existing ethical discussions on issues specific to pediatric clinical research.

The European legal framework

The urgent need to conduct clinical research in minors has called for legislative action. In Europe, various regulations have been promulgated by diverse legislative bodies over the past decade, aiming at the facilitation and promotion of pediatric research and the harmonization of standards of good clinical practice.

In this article, three criteria are used to determine the scope of relevant legislation. First, the scope is limited to legislation issued at the European level (i.e., the European Union or Council of Europe). Domestic legislation of individual countries is thus not taken into account. Second, the scope is limited to legal provisions that are related to ethical concerns in the conduct of pediatric clinical trials. By consequence, regulation focusing on administrative or technical issues such as the production of investigational medicinal products or the labeling of drugs falls outside the scope of this article. Third, only provisions specifically addressing the involvement of minors in clinical trials fall within the scope of this article. General provisions regulating the involvement of competent adults in research are not discussed exhaustively, although these provisions may also apply to the involvement of minors in clinical trials. In accordance to these criteria, the European Convention on Human Rights and Biomedicine, the European Clinical Trial Directive, and the Pediatric Regulation fall within the scope of this article.

European Convention on human rights and biomedicine

In 1997, the Council of Europe promulgated the European Convention (European Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine).[8] In 2005, this convention was supplemented with an additional protocol on biomedical research (Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research, Strasbourg, 25 January 2005).[9] To date, the European Convention is binding upon the 13 EU member states (and eight countries outside the EU) that signed and ratified it, and its additional protocol is

binding upon the four EU member states (and one country outside the EU) that signed and ratified it.[i]

The European Convention specifically addresses the issue of pediatric research in article 17. Also, articles 6 and 16 are of some relevance, as they provide details on the protection of persons not able to consent (be it not specifically in the setting of clinical research) and the protection of persons undergoing research (be it not specifically minors), respectively. The additional protocol on biomedical research touches on the subject of pediatric research in article 17.

European clinical trial directive

The European Directive (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of laws, regulations and administrative provisions of the member states in relation to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)[10] mainly aims at a harmonization of the provisions regarding good clinical practice and the facilitation of multicenter clinical trials across the borders of individual EU member states. All EU member states were bound to implement this directive into national law before the deadline of 1 May 2004. In the national implementation of the European Directive, EU member states were free to adopt stricter provisions than those set down in the European Directive, as long as the standards of protection and time limits captured in the European Directive were not violated (article 3,1). The European Directive specifically addresses the issue of involving minors in research in article 4.

In addition to the provisions of the European Directive, the scientific guidelines of the European Medicines Agency (EMEA) must be followed. In this respect, the guideline "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population"[11] was recently issued by EMEA to guide the implementation of the European Directive in pediatric research practice.

Pediatric Regulation

Even though the European Directive was a milestone in the facilitation of clinical trials, further legislative initiatives were needed to address the lack of interest in developing drugs for the young. To correct the disinterest of the industry in developing and marketing drugs for children, the Pediatric Regulation (EU Regulation 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Pediatric Use and Amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004)[12] requires that clinical trials in minors be planned and conducted for all new products entering the market. In addition, the Pediatric Regulation

[i] A list of countries that signed and/or ratified the convention can be consulted at: http://conventions.coe.int/Treaty/Commun/ChercheSig. asp?NT=164&CM=&DF=&CL=ENG.

offers considerable rewards for the conduct of clinical trials in minors, in the form of prolongation of market exclusivity. In contrast to the European Convention and the European Directive, the Pediatric Regulation is entirely dedicated to clinical research in minors.

Ethical principles and pediatric clinical research conduct

Various types of bioethical reflection can be used to identify, clarify, and discuss ethical issues in pediatric research. In this paper, a principle-based approach will be used as a conceptual framework to interconnect (1) the main ethical issues in involving human persons in research, (2) the common approaches of these issues in competent adults, (3) the workability problems these paradigmatic approaches have in the pediatric research setting, and (4) the regulatory answers to these workability problems.

Although principles are a well-validated tool for ethical reflection, their generality may render them somewhat difficult to apply directly to specific ethical issues. Therefore, in this article, the four principles of biomedical ethics—justice, non-maleficence, beneficence, and autonomy[7]— will be tailored to the specific issues of involving minors in research by describing them in terms of four fields of social, scientific, and regulatory action. Obviously, overlap between these four fields of action will exist, as the four principles cannot be distinguished strictly from each other in content and scope.

Justice

The formal principle of justice can be set forth in several ways: to each person an equal share or a share according to (1) need, (2) effort, (3) contribution, (4) merit, and (5) free market exchanges.[7]

Obviously, the unmet medical needs of minors are a major reason to encourage the development of safe and efficacious drugs for the young. Free market exchanges are also relevant to the development and provision of safe and efficacious drugs for children, as the pharmaceutical industry is a key player in this process. In contrast, effort, contribution, and merit are not commonly cited as motives to develop and distribute drugs for pediatric patients. Therefore, in this article, the principle of justice will be referred to as a "share according to need" and a "share according to free market exchanges."

Main issues in clinical research and paradigmatic approach in competent adults

To respond to existing therapeutic needs, safe and efficacious drugs must be developed and made available to patients who can benefit from them. The development, safety, efficacy, and availability of drugs all entail ethical issues.

The current paradigmatic approach leaves the development and distribution of drugs in large part to the market. Requirements for obtaining marketing authorization seek to guarantee that drugs are safe and efficacious. According to these requirements, the terms of use must be captured in the corresponding license that provides details of the patients,

ages, indications, dosages, routes of administration, and contraindications associated with each drug.[13]

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of justice

While requirements for obtaining marketing authorization are effective to assure the safety and efficacy of drugs that enters the market, these requirements fail to supply the population of minors with an equitable variety of drugs.

Due to the high complexity of testing drugs in children, the costs of testing a drug in minors may well exceed the potential return on investment and, therefore, render it economically unattractive to label drugs for pediatric use. As a result, there is a dearth lack of drugs for use in children, and in many instances, pediatricians have no therapeutic options apart from using drugs off-license or off-label.[14] The high rate of off-license and off-label drug prescriptions in pediatric practice is disturbing, as it entails experimental drug use outside of the controlled conditions of a clinical trial.[15]

In the ongoing efforts to develop and provide drugs for the young, the principle of justice is made operational in the pediatric research setting as the provision of safe and efficacious treatments for minors.

Non-maleficence

The principle of non-maleficence intimates that biomedical interventions should not intentionally inflict harm on the subjects of these interventions. This principle is often formulated as “first do no harm” (*primum non nocere*).

Main issues in clinical research and paradigmatic approach in competent adults

The numerous incidences of unethical research conduct that have occurred in the past century indicate that research can be unsafe, disrespectful of established ethical guidelines, and lacking in scientific quality.[16]

Central to the current paradigmatic approach of unethical research is the review of research protocols by ethics committees. This procedure seeks to guard that research has added value, is safe and scientifically sound, and pays sufficient attention to ethical issues such as the provision of information and the protection of the research subjects.

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of non-maleficence

In pediatric research, the desire to prevent unethical research can obstruct or prevent the development of drugs for pediatric use, as the act of balancing the protection of minors and the promotion of medical progress has proven to be complicated in the past several decades.[17] Therefore, pediatric expertise in ethics committees is essential in addressing the specific complexities of involving minors in clinical trials.

In the specific setting of pediatric research, the principle of non-maleficence is made operational in the well-organized efforts to prevent unethical research, among which the review of research protocols by an ethics committee.

Beneficence

While the principle of non-maleficence requires that biomedical interventions do not inflict harm on the persons undergoing these interventions, the principle of beneficence requires that biomedical interventions contribute to the welfare of these persons. This can be achieved in two ways. First, biomedical interventions can generate benefits in the research subjects themselves. Second, the drawbacks of biomedical interventions can be balanced with a newly generated benefit, either directly to the minor research subject or to another beneficiary.

Main issues in clinical research and paradigmatic approach in competent adults

The principle of beneficence is not easily applicable to research in humans. While a medical intervention that is not intended to cause a direct benefit to the individual concerned would be considered futile in the context of a treatment, the situation is clearly different in the context of research. Research does not necessarily aim at generating a direct benefit to the research subject. In the absence of a benefit, however, there is no counterbalance for the risks and/or burdens involved in research.

Paradigmatically, competent persons are considered to be capable of voluntarily accepting the risks and/or burdens involved in research. Therefore, the absence of a benefit need not be a hurdle to conducting valuable non-beneficial research.

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of beneficence

Most minors are incapable of informed consent. As a consequence, a third party (the parents or another legal representative) has to decide upon the participation of a minor in a clinical trial. This proxy decision maker must serve the interests of the minor. When there is no benefit to counterbalance the risks and burdens involved in participating in the research, the interests of the minor in participation may be hard to demonstrate and the risks and burdens involved may be difficult to justify.

Given the strong emphasis on risks in research participation, the principle of beneficence is made operational in pediatric research in the efforts to counterbalance risks and burdens involved in research participation.

Autonomy

The principle of autonomy is closely related to the capacity for self-governance of competent human beings. This capacity enables individuals to make autonomous decisions that should be respected by others.

Main issues in clinical research and paradigmatic approach in competent adults

In clinical research, autonomous decision makers are often, paradoxically, highly dependent upon others, as they need information provided by experts to make rational and informed decisions.[18] However, the information provided can be biased, deceptive, or misunderstood (e.g., in case of therapeutic misconception, see.[19] [20] As a result, autonomous decision-making may be compromised.

In competent adults, the ethical and legal doctrine of voluntary and informed consent is used as a paradigm for autonomous decision-making. According to this doctrine, valid decisions to participate in research must be made voluntarily by competent persons (or their representatives) after being duly informed of the nature, significance, implications, and risks involved in the research. As a general rule, informed consent for research participation must be provided in writing. The doctrine of voluntary and informed consent is well validated in ethics and law.

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of autonomy

In the pediatric setting, most research subjects are not capable of making autonomous decisions because they do not comply with the ethical and legal requirements to do so. The fact that most minors are incapable of giving a legally valid consent, however, does not preclude them from having certain decision-making skills, such as understanding what the decision is about, assessing information, and making rational decisions.

In decisions to enroll a minor in clinical a study, different participants negotiate their varying interests and concerns The role minors can and should play in these decisions may be hard to determine due to the constantly evolving capacities and maturity of minors. However, the principle of respect for minors implies that minors are appropriately involved in decisions about research participation. Therefore, in pediatric research, the principle of autonomy is made operational in pediatric research as respect for the minor by means of a fair distribution of power and responsibility in research participation decisions.

Ethical concerns addressed in the European legal framework

All four ethical concerns in pediatric research discussed above are addressed in various documents of the European legal framework. We will now explore how these ethical concerns are addressed in the content of the European legal framework.

The European Convention on human rights and biomedicine

The European Convention's provisions regarding the involvement of minors in clinical research are related to the ethical concerns of counterbalancing risks and burdens, preventing unethical research, and distributing decision-making power and responsibility fairly.

Counterbalancing risks and burdens

As a general rule, article 17,1ii of the European Convention provides that research on a person without the capacity to consent may only be undertaken if "the results of the research have the potential to produce real and direct benefit to his or her health." In the absence of a real and direct benefit, the risks and burdens are only deemed acceptable if two additional requirements are met. First, the research must aim at generating benefit to persons sharing the same age category, disease, disorder, or condition with the participating research subject (article 17,2i). Second, research may only entail minimal risk and minimal burden to the research subject involved (article 17,2i). In the additional protocol, the terms "minimal risk" and "minimal burden" are clarified. According to article 17 of the additional protocol, a research intervention only entails minimal risk if the results of that intervention generate, at the most, a very slight and temporary negative impact on the health of the person concerned and it entails only minimal burden if it is to be expected that the discomfort to the research participant will be, at the most, temporary and very slight. The explanatory report illustrates minimal risk as taking a single blood sample from a child (Explanatory Report, section 111).

The double requirement of generating a group benefit and limiting risks and burdens to no more than "minimal" puts strong boundaries on pediatric research. In accordance with the European Convention, several research interventions, such as clinical trials in early stages of drug development, are not permitted in children.

Preventing unethical research

The prevention of unethical research is also addressed in the European Convention. First, the convention states that minors should only take part in clinical research if similar results cannot be obtained without their involvement, i.e., by research not involving humans (article 16,i) or by research involving individuals capable of informed consent (article 17,1iii). Second, article 17,1iv requires that authorization must be provided specifically and in writing.

Fair distribution of decisional power and responsibilities

The European Convention requires in article 17,1iv that the representative of the minor must grant his or her informed consent for the involvement of a minor in a clinical trial. Although the European Convention requires that the opinion of minors must be taken into consideration as an increasingly determining factor in relation to age and degree of maturity regarding therapeutic interventions (article 6,2), this provision does not occur in the provisions on research participation. However, the active participation of minors in decisions is not hereby precluded. On the contrary, the European Convention grants minors a veto right, as it is provided in article 17,1v, that research can only be carried out if the minor research subject does not object.

The European clinical trial directive

Like the European Convention, the European Directive delineates specific provisions regarding the involvement of minors in clinical research (article 4) and touches on the ethical concerns of counterbalancing risks and burdens, preventing unethical research, and fairly distributing decision-making power and responsibility.

Counterbalancing risks and burdens

The European Directive provides for a counterbalance to the risks and burdens involved in pediatric research by requiring that the research generate a direct benefit. In article 4e, this direct benefit is defined broadly as "some direct benefit" that can be either an individual benefit (to the research subject) or a group benefit (to the group of patients). In the case of a group benefit, no additional requirements are applicable.

Along with the requirement that research generate a benefit, the European Directive also sets forth a preventive measure in article 4g, requiring that clinical trials be designed to "minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage." The requirement that the degree of distress and risk be constantly monitored, as stated in the same article, demonstrates the importance of this provision, as conformity with most requirements in the European Directive is only assessed at a single point in time.

Prevention of unethical research

The protection of minor research subjects is extensively addressed in the European Directive. Aiming at the harmonization of already existing guidelines on good clinical practice, the directive integrates the myriad principles captured in the historical codes of research ethics in which the protection of research subjects has consequently been a vast priority.

First, the well-known general principle that the interests of the patient always prevail over those of science and society is adopted in article 4i of the directive. This provision is notably subsumed in the specific provisions on clinical trials on minors.

Second, the European Directive states that minors should only be involved in research if there is a necessity to do so. Consequently, minors should not be involved in research when similar results can be obtained by research in competent adults or by other research methods, as provided in article 4e. In addition, this article requires that research be related directly to "a clinical condition from which the minor concerned suffers or be of such nature that it can only be carried out on minors."

Third, article 4a of the European Directive requires that consent for research participation is given by the parents or a legal representative. It is specified that consent "must represent the presumed will of the minor, and may be revoked at any time without repercussions to the minor."

Fourth, according to article 4d of the European Directive, incentives or financial inducements to stimulate research participation, except for compensation, are prohibited.

Finally, article 4h of the European Directive requires that an ethics committee with pediatric expertise ("or after taking advice in clinical, ethical, and psychosocial problems in the field of pediatrics") endorse the research protocol. This ethics committee faces the challenging task of assessing whether the design of the research project sufficiently fulfills the ethical requirements captured in the European Directive.

Distributing decision-making power and responsibilities fairly

The European Directive serves the involvement of minors in decisions on research participation by stating in article 4b that minors must receive information "regarding the trial, the risks, and the benefits of the trial," in accordance with their capacity for understanding and provided by staff with experience with minors. In addition, article 4c provides that the (principal) investigator must consider the explicit wish to refuse or discontinue participation formulated by a minor who is capable of assessing information and forming an opinion.

The guideline on the implementation of the European Directive issued by the EMEA (Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population) provides additional guidance in the fair distribution of power and responsibilities among decision makers. This guideline addresses a number of important issues in the involvement of minors in clinical trials. First, assent, a term that is not used in the European Directive, is recommended in the additional guidance as a means to enable the participation of minors in decisions. Notwithstanding this provision, the responsibility of parents to protect the interests of their child is emphasized.

Second, the gray zone between legal capacity to consent and factual capacity is addressed. It is acknowledged that certain minors are mature enough to provide valid consent, even when they have not reached the legal age cutoff. In this respect, the guideline acknowledges that "emancipated minors" must give written consent to participation in research and that the consent of the parents or another legal representative is not required for mature minors. Notwithstanding this provision, it is emphasized that mature minors can be vulnerable and may require additional discussions and explanations.

The pediatric regulation

The Pediatric Regulation solely addresses the issue of involving minors in clinical research and focuses on the issue of facilitating the development of safe and efficacious are for minors of all ages. In article 2,1 of the regulation, minors are defined as the population between birth and 18 years of age.

The provision of safe and efficacious treatments to children

To encourage pediatric research aiming at the development of new drugs, the Pediatric Regulation requires that, for every request for marketing authorization, a Pediatric

Investigation Plan (PIP) be negotiated early in the research (article 7). This PIP is to ensure that the data necessary to use a drug in all subsets of the pediatric population are gathered in the clinical research preceding the marketing authorization. However, waivers and deferrals to this general rule are possible under certain conditions. In addition, pediatric research is encouraged by means of strong incentives, as drugs tested in children obtain an extension of market exclusivity of 6 months (article 36). Also, for off-patent drugs, research in minors is rewarded by means of the "pediatric use marketing authorization."

To arrange the assessment of PIPs, waivers, and deferrals, article 3 of the Pediatric Regulation mandates the establishment of a Pediatric Committee, whose main tasks are the assessment of PIPs, waivers, and deferrals and the support and advice of the agency and commission.

Comparative analysis of the legal framework

The European legal framework surrounding pediatric clinical trials addresses various ethical issues. However, none of the individual documents that constitute the framework addresses the major issues in pediatric research in a systematic and exhaustive way. While the European Convention and the European Directive mainly focus on the counterbalancing of risks and burdens, the prevention of unethical research, and the fair distribution of powers and responsibilities in decision making of research participation, the Pediatric Regulation focuses almost exclusively on the development and provision of safe and efficacious drugs for minors.

Unfortunately, the European legal framework lacks internal consistency in certain matters. A comparative analysis of the three main documents of the European legal framework reveals contradictory provisions among the different documents, such as the provisions regarding non-beneficial research and the veto power of minors in decisions of research participation. In the area of non-beneficial research, article 17,2 of the European Convention requires that, in the absence of a direct benefit to the individual research participant, a minor can be involved in research if the study only entails minimal risks and minimal burden, while article 4e of the European Directive simply requires "some direct benefit" to the research subject or a related group of beneficiaries. This indicates that the European Convention endorses a more restrictive policy than the European Directive. Consequently, early stage drug development may be compromised in member states that have signed and ratified the European Convention.

In relation to the power of a minor to veto participation in clinical research, contradictory provisions also exist. While article 4c of the European Directive states that the (principal) investigator must consider the explicit wish of a minor to refuse or discontinue participation (given that the minor is capable of assessing information and forming an opinion), article 17,1v of the European Convention states that minors cannot be involved in a study when they object to research participation. Thus, the European Convention theoretically grants minors more extensive decision-making power than the European Directive does.

In addition to these contradictory provisions, the European legal framework contains numerous contingencies that require extensive interpretation. It is not clear, for example, what must be understood to be an acceptable risk– benefit ratio, what it means to "consider" the explicit dissent of a minor, how the capacity of minors to make decision can be assessed, or why the European Directive refers to minor research participants as "patients" and links benefits to the "group of patients." The fact that many terms are not clearly defined is likely to negatively affect the implementation of the European legal framework and creates the need for accurate guidance and support.

The interpretation and application of principles and requirements are largely left to those active in the field of pediatric research practice. Although it is true that efforts have been made to provide additional guidance in the interpretation and implementation of the legal framework, little practical support is offered to those responsible for implementing the law.

Discussion: ethical concerns in regulating clinical trials

Up to this point, we have integrated the (1) ethical issues in clinical research, (2) common approaches to these issues in competent adults, (3) workability problems of these paradigmatic approaches in the pediatric research setting, and (4) regulatory answers to these problems. Now, we will discuss the regulation of the ethical concerns in pediatric research and to relate our analysis of the European legal framework to specific discussions in bioethics.

The development of safe and efficacious healthcare for minors

Throughout this article, it has been clarified that the lack of commercial interest in testing drugs in minors must be corrected in order to guarantee the marketing of an equitable variety of drugs for pediatric use. Such a correction has been effected in the European legal framework, as the Pediatric Regulation offers an extension of market exclusivity as a reward for the conduct of pediatric clinical trials.

This incentive provided for in the Pediatric Regulation, however, is open to discussion on two counts. First, it is questionable whether the extension of market exclusivity is a reasonable and fair incentive. While the extension of market exclusivity seeks to compensate the high costs of pediatric trials, the actual profits generated as a result of this incentive are highly variable; in some cases, the extension of exclusivity not even compensates for the costs of conducting the trial, while in other cases, the conduct of pediatric trials is a lucrative enterprise.[ii] This highly variable compensation for the costs of

[ii] Similar to the Pediatric Regulation, US Legislation offers (already since 1997) a 6-month extension of marketing exclusivity as a reward for the conduct of pediatric clinical trials. A study of the economic return of the Pediatric Exclusivity Program in the US shows that the economic return of the 6-month exclusivity

conducting pediatric trials challenges the fairness and effectiveness of this incentive. Second, an extension of market exclusivity may also work against the quality of research. As the extended exclusivity is granted regardless of the results of pediatric research (and the marketing of a drug for use in pediatrics), pediatric trials may be more economically oriented than healthcare oriented. Care must be taken to ensure that the incentives provided for in the Pediatric Regulation encourage the actual marketing of drugs for use in children and do not result in the pro forma conducting of pediatric trials, which are aimed at acquiring the reward than actually marketing drugs.

Counterbalancing risks and burdens

To prevent the interests of minors from being harmed in the process of proxy consent provided by the parents or another legal representative, the freedom to accept the risks and burdens of voluntarily participation in research is strongly restricted in pediatric research (cf. supra). The main restriction of this freedom is the fact that research in minors must aim at generating a benefit for the research participant or for a related group of beneficiaries. This strong emphasis on benefit engenders several ethical issues.

First, even though children have an understanding of the risks and benefits of research,[21] it is hard to measure benefit, risk, and burdens in a reliable way or to assess their proportionality. Although risks may be determined using objective toxicity criteria, the benefits, risks, and burdens in research are not entirely objective standards. On the contrary, the experience and interpretation of risks, burdens, and benefits is highly personal and related to the condition, disease, and personal experience of the participant. Due to this subjective nature, it is not clear how risks, burdens, and benefits can be assessed in a reliable way and how the proportionality between risks and burdens can be determined. Second, the strong emphasis on benefit blurs the distinction between research and therapy. While the distinction between research and therapy was already flawed in pediatric practice due to the high rate of off-label treatments (which constitutes, to a certain extent, an experimental use of drugs), the strong emphasis on the necessity of a therapeutic benefit in pediatric research gives the impression that research is a kind of a pseudotherapy. This may result in a therapeutic misconception in the minds of minors and their parents.

Third, the requirement that research should generate a benefit imposes strong boundaries on altruistic behavior in minors. While it is commonly rejected that minors have a duty to participate in research, minors may be willing to participate in research for altruistic motives. However, the strong emphasis on benefit and the restrictions on non-beneficial research may constitute a hurdle to altruistic behavior in research participation. Therefore, one could reasonably ask whether pediatric research should not be opened up for altruistic behavior by (healthy) volunteers or patients not belonging to the group of

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extension is highly variable with net return-to-cost ratios ranging from −0.84 (i.e., a loss of $11,088,214) to 73.63 (i.e., a profit of $507,899,374) (see Li et al. [23]).

expected beneficiaries.[22] Enabling minors to decide upon voluntary participation in non-beneficial research themselves, however, remains ethically contested.[23]

Fourth, incentives continue to be a sensitive issue.[24] [25] While it is generally recognized that no financial incentives other than compensation for the costs involved in research participation is ethically acceptable, it is not clear how difficulties in the recruitment of research subjects can be addressed without using incentives. In pediatric research, there is the additional complexity that a reasonable compensation of costs may appear to be a large amount of money to a minor.

The prevention of unethical research

The prevention of unethical research is arranged effectively. The numerous historical incidences of unethical research in human beings in general and minors in particular have called for response in court trials (e.g., the Nuremberg Trials), self-regulatory efforts of the medical community (e.g., the World Medical Association's Declaration of Helsinki), harmonized guidelines on good clinical practice (e.g., International Conference on Harmonization (ICH) E6, E11), and legal regulation (e.g., European Convention, European Directive).

The fair distribution of power and responsibilities in decision making on research participation

Central to research participation is the voluntary and informed consent granted by the research participant. In pediatric research, however, such consent most often cannot be obtained, as most minors are incapable of legally valid consent. The problems of implementation that the ethical and legal doctrine of voluntary and informed consent face in the setting of pediatric research are commonly addressed by diversifying the process of informed consent. This diversification may entail proxy consent given by the parents or another legal representative, assent or dissent by the child, and the provision of appropriate information to minors.[26] [27]

While the diversification of consent successfully tailors the legal dimension of informed consent to the pediatric setting, it fails to address the ethical dimension of consent in a satisfactory way, as the ethical principle of respect for persons that underpins the doctrine of informed consent is eroded by such a diversification. Transferring the power to consent from the research subject to a third party distracts the attention from the central position of the minor in decisions on research participation, while there is no reason to compromise the principle of respect for persons in the pediatric setting.[28] Therefore, the active involvement of the minor in decisions to participate in research should not be an affirmation of a decision that was already made by the parents (as is the case in parental consent and assent of the child), but the starting point of decisions on research participation whenever possible (which may not be the case in small children).

Although the European legal framework recognizes that minors develop a growing capacity to understand and assess information and make informed decisions, the exact role

that is attributed to minors in decisions on research participation often remains unclear. While the right of minors to be informed and to dissent is taken very seriously, there is no clarity concerning the active role that minors can and should play in the actual decision-making process apart from affirming or refusing participation. In addition, it is hard to determine the decision-making capacities of individual minors.[29] Therefore, practical support for the active involvement of minors in decisions on research participation could be of great help in making the principle of respect for persons operational in the setting of pediatric research.

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Chapter 2: Domestic regulation of EU Member States

Pinxten, W., Dierickx, K., Nys, H. (2010) Diversified Harmony, Supranational and domestic regulation of pediatric clinical trials in the European Union, Journal of Cystic Fibrosis. [accepted]

Abstract

Over the past decades, considerable legislative effort has been made to facilitate and encourage clinical research in the European Union (EU). Hereby, specific attention has been paid to the urgent need to conduct research in minors. In this article, we will analyze the regulation that currently governs pediatric clinical research conduct at the supranational level of the EU and at the level of individual EU member states. Our analysis will focus on the way in which the national and supranational legal frameworks address five ethical issues that are specific to pediatric clinical research: (a) informed consent, (b) the necessity to conduct research in minor subjects, (c) the interests of the subject concerned, (d) the risks and burdens involved, and (e) the pediatric expertise of protocol review committees. We conclude by discussing the harmonization and diversification of the legal requirements that govern pediatric clinical research in the EU.

Introduction

Safe and efficacious drugs cannot be provided to those in need without the conduct of clinical research. Over the past decades, considerable legislative effort has been made to facilitate and encourage the conduct of clinical research in the European Union (EU). Hereby, specific attention has been paid to the urgent need to conduct research in small and vulnerable populations in general and minors in particular.

At present, pediatrics is still hampered by a stringent lack of licensed drugs that are labeled for pediatric use. Although minors have been designated as therapeutic orphans ever since this phenomenon was first described in 1968,[1] the gamut of approved medicines for use in children remains considerably smaller than that available to adults.[2-4] Nonetheless, catching up with pediatric research is a precarious enterprise, and several constraints render the conduct of clinical studies in minor subjects complicated and expensive.[5]

In the specific case of cystic fibrosis, the conduct of clinical research in minor subjects is particularly valuable for several reasons. First, starting with preventive and therapeutic measures at an early stage of the disease is an important asset because the pathology of cystic fibrosis develops over time. Therefore, the disease will have caused less irreversible damage to the body in young children than in adults, and early intervention may open up additional therapeutic opportunities. Second, the treatment of CF involves considerable drug intake, also for minors. The availability of safe and efficacious drugs is thus of great importance to minors suffering from CF. In addition, clinical trials may result in a reduction

of the number of drugs that CF-patients need to take, and thus reduce the burden of the often harsh- therapeutic scheme. Third, the number of patients with CF is relatively large, rendering the population a good candidate for the conduct of pediatric clinical research. The population of CF minors is not too small to compound representative samples of research subjects, and the market for newly tested medicines can be large enough to make research financially viable.

Obviously, the conduct of clinical research in the vulnerable population of minors generates abundant, diverse, and specific ethical issues. Nonetheless, these issues have increasingly been addressed in the ethical and legal frameworks that currently govern clinical research in the EU.[5]

In this article, we will analyze the regulation that currently governs pediatric clinical research conduct at the supranational level of the EU and at the level of individual EU member states. Our analysis will focus on the way in which the national and supranational legal frameworks address five ethical issues that are specific to pediatric clinical research: (a) informed consent, (b) the necessity to conduct research in minor subjects, (c) the interests of the subject concerned, (d) the risks and burdens involved, and (e) the pediatric expertise in committees that review research protocols for pediatric studies. Our analysis concludes with a discussion of the harmonization and diversification of the legal requirements that govern pediatric clinical research in the European Union.

Scope, Materials and Methods

In this article, the supranational and national legal frameworks that govern pediatric clinical research in the EU are investigated. Several criteria were used to determine the scope of our analysis. First, our analysis is limited to legislation that was issued under the responsibility of either the European Union, the Council of Europe, or by a legislative body of an individual EU Member State. Second, only legal regulations fall within the scope of our analysis. Ethical codes that were not promulgated by a legislative body, such as the Declaration of Helsinki, are thus not taken into account, even though these codes may have considerable (moral) authority. Third, to be part of our analysis, regulation must concern the ethics of pediatric research conduct, and thus be related to good clinical practice in pediatric research conduct or the encouragement and facilitation of pediatric clinical research. Therefore, purely administrative requirements fall outside the scope of our analysis, even when they are specific to pediatric research. Likewise, the general requirements for good clinical practice in research conduct that are also applicable to other patient populations will not explicitly be part of our analysis, even though these requirements are often applicable to research in minor subjects. Also the general procedures of protocol approval by ethics committees or competent authorities in individual EU member states will not be the subject of our analysis, as such analysis was already published elsewhere.[6 7]

At the supranational level, the Clinical Trial Directive (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of laws, regulations and administrative provisions of the member states in relation to the

implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use) functions as the centerpiece of a wider regulatory framework.[8] In addition to the Clinical Trial Directive, the Pediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004) is highly relevant for the conduct of pediatric clinical research in EU Member states.[9] This regulation discusses the conduct of ethical research and aims to encourage and reward the conduct of pediatric clinical research. Third, the Council of Europe Convention on Human Rights and Biomedicine (European Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine, Oviedo 1997, further the European Convention)[10] is binding upon the EU member states that respectively signed and ratified the Convention.[i] In 2005, the European Convention was supplemented with an additional protocol on biomedical research (Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25.I.2005),[11] which is binding upon the member states that signed and ratified this additional protocol.[ii]

In addition to our analysis of supranational regulation, we analyzed the domestic legislation that implements the Clinical Trial Directive into the national law of individual EU member states. Table 1 offers an overview of national laws implementing the Clinical Trial Directive. The original texts of domestic laws, acts, decrees, or regulations that implement the Clinical Trial Directive into national law entail different legal systems (civil law and common law) and are issued in no less than 22 different languages. Our analysis covers original texts in four languages (English, French, German, and Dutch). In addition, (most often unauthorized) English translations of national laws were consulted, and in one case, a native speaker was called upon to gather information where no translation was accessible.[iii]

For 24 EU Member States, the text of the national law that implements the Clinical Trial Directive could be analyzed in its original language or via an (unauthorized) English translation. Specific regulations arranging the operational implementation of national laws (e.g., (royal) decrees, orders, circulars), however, were often difficult or impossible to access in English. Therefore, these documents will not exhaustively be part of the analysis presented in this article. For three countries, there was no English translation of the national

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[i] For an overview of countries that signed and ratified the European Convention, see: http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=&DF=&CL=ENG (accessed: 1 December 2009)

[ii] For an overview of countries that signed and ratified the European Convention's Additional Protocol concerning Biomedical Research, see: http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=195&CM=7&DF=03/12/2009&CL=ENG (accessed: 1 December 2009)

[iii] The authors are grateful to Zuzanna Osewska for the analysis and translation of the Polish law.

law implementing the European Clinical Trial Directive available (Cyprus, Hungary, and Slovenia). For these countries, the analysis in this article is based on secondary sources, in so far that such information could be traced.

Table 1:
Overview of the national laws implementing the European Clinical Trial Directive

Country	Domestic implementation of Directive 2001/20/EC[iv]	Article
Austria	Drug Law (1983, amended 29 April 2004 to implement Directive 2001/20/EC)	§42(1)
Belgium	Law concerning experiments on the human person (7 May 2004)	Art. 7
Bulgaria	Medicinal Products in Human Medicine Act (13 April 2007).	Art 97, 100
	Regulation No. 31 on the Rules for GCP (12 August 2007) is applicable.	
Cyprus	-	
Czech Republic	Act on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals, 6 December 2007).	Section 52
	Decree on good clinical practice and detailed conditions of clinical trials on medicinal products (23 June 2008).	Section 8 (5)
Denmark	Act on a Scientific Ethical Committee System and the Processing of Biomedical Research Projects (28 May 2003).	Art. 17 Art. 19
Estonia	Medicinal Products Act (16 December 2004).	§91
Germany	Medicinal Products Act (12 December 2005).	Chapter 6, Section 40(4) and 41(2)
Finland	Medical Research Act No. 488/1999 (23 April 2004).	Section 8
France	Law no. 2004-806 of 9 August 2004 concerning public health policy	1121-1122
Greece	Law n° DYG 3/89292 on the harmonization of the Hellenic Legislation to the respective Community legislation in compliance with Directive 2001/20/EC of 4 April 2001 "on the approximation of the legislative, regulatory and administrative provisions of the Member States regarding the implementation of Good Clinical Practice (GCP) in clinical trials on medicinal products for human use". (12 December 2005).	Art. 4

[iv] The document named in the list is the main law, act or regulation implementing the Clinical Trial Directive into the national law of the member state concerned, that has explicitly been drafted to implement the Clinical Trial Directive. It is important to acknowledge that other laws, acts or regulations that are complementary to the named document(s) in the regulation of pediatric research may exist.

Hungary	Health Ministry Decree EüM24/2002 on the clinical trial of medicinal products for human use and on Good Clinical Practice	
Ireland	Statutory Instrument No. 190 of 2004 (European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations (29 April 2004).	Part 4
Italy	Legislative Decree no. 211 concerning the transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use (24 June 2003)	Section 4
Latvia	Cabinet Regulation No 172 Regulations on Conducting Clinical Trials and Non-interventional studies and Labeling of Investigational Medicinal Products, and Procedure for Conducting Inspections on Compliance with the Requirements of Good Clinical Practice (28 February 2006).	Art. 30
Lithuania	Health Care Ministry Decree on the Implementation of the Rules of Good Clinical Practice, which implemented Directive 2001/20/EC (11 May 2004).	
	Law on Ethics of Biomedical Research (11 May 2000).	Art. 7
Luxembourg	Grand Ducal Regulation concerning the application of good clinical practice in the conduct of clinical trials of medicines for human use (Clinical Trials of Medicines for Human Use, 30 May 2005).	Art. 4 Art. 6
Malta	Amended Medicines Act (Medicines act to make provision for matters connected with the manufacture, preparation and assembly, wholesale distribution, storage, destruction, disposal, advertising and authorization of medicinal products and any activity connected therewith and the regulation of the sale of medicinal products, pharmacies and related pharmaceutical activities and for any other matters ancillary thereto or connected therewith, 21 November 2003)	Art. 18.2.
Netherlands	Amended Medicinal Research involving Human Subjects Act (Regulations on medical research involving human Subjects, 1 March 2006).	Section 6
Poland	Resolution of the Senate of the Republic of Poland of 16 April 2004, amending the Pharmaceutical Law and the Act on the Profession of the Medical Doctor	
Portugal	Law no. 46/2004 concerning Clinical Trials on Medicinal Products for Human Use (19 August 2004).	Art. 7
Romania	Ministry of Health order No. 904/25.07.2006 on approval of rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use	
Slovakia	Ministerial Decree on clinical trials and Good Clinical Practice (1 May 2004).	Art. 15b
Slovenia	-	

Spain	Royal Decree 223/2004 regulating clinical trials with medicinal products (6 February 2004).	Art. 4 Art. 7,3
Sweden	Act concerning the Ethical Review of Research Involving Humans (5 June 2003).	Section 18
United Kingdom	Medicines for Human Use (Clinical Trials) Regulations (Statutory Instrument 2004 No. 1031, 31 March 2004).	Part 4

1. Ethical issues addressed in the legal frameworks

Five major ethical issues in pediatric clinical research conduct are addressed in the European legal frameworks governing pediatric research: (a) informed consent, (b) the necessity to conduct research in minors, (c) the interests of the research subject in the study concerned, (d) the risks and burdens involved, and (e) the pediatric expertise of ethics committees reviewing protocols for clinical studies in minors.

1.1 Informed consent

Ever since the research scandals during the Second World War and its aftermath, the principle of respect for persons has been adopted steadfastly in influential ethical guidelines and legal regulations. Traditionally, this principle has been made operational in the ethical and legal doctrine of informed consent.

The current paradigm of informed consent for research participation is voluntary consent provided by a legally competent adult after being duly informed about all relevant aspects of the clinical trial concerned. For several reasons, this paradigm has serious workability problems in the case of pediatric clinical studies. First, due to age restrictions, most minors are not capable of granting legally valid consent, as they may not have reached the age of medical majority (which is not necessarily the same as the age of legal majority).[12] Second, the capacity to understand and assess information is often still underdeveloped in minor research subjects. As a result, minors may lack the competence necessary to make rational decisions and it may be difficult to inform minors duly. Third, most minors are largely dependent upon their parents in numerous aspects of their lives. It is widely recognized that parents enjoy considerable discretion in educational matters, and therefore they may, to a large extent, decide autonomously whether and to what extent their minor children can participate in decisions about clinical trial participation.

Due to the incompetence of minors to provide legally valid informed consent, the involvement of a competent adult acting as a surrogate decision maker is most often required to enroll a minor in a clinical trial. Obviously, such involvement of a proxy does not preclude minors from playing an active role in decisions about clinical trial participation. Quite the reverse, several decision making strategies, including (i) dual consent, (ii) consent by the proxy and assent by the child, and (iii) respect for the dissent of the child, aim at encouraging shared decision making and a fair differentiation of decision authority between the proxy decision maker and the minor research subject.

1.2 Necessity to involve minors

Minors are widely regarded as a vulnerable population that deserve extensive protection against harm and abuse. Therefore, it is a generally accepted principle that minors should not be exposed to the risks to harm and abuse that are inherent to any clinical trial, unless this is strictly required to generate relevant research results that will be of benefit to minor patients. In this respect, the large majority of ethical codes and legal rules prohibit research from being conducted in minors whenever alternative research methods or (non-vulnerable) populations are available.

1.3 Interest in the research

To preclude human subjects who participate in clinical trials being used as a means to procure a scientific end, two principles of research conduct are generally adopted in the ethical codes and legal regulations governing clinical research. First, the principle that the interests of science and society never prevail over the interests of individual research subjects is widely endorsed in ethics and law. Second, it is widely assumed that research should comply with the interests of the subjects involved. However, it is important to emphasize that these interests can be very broad and diverse, as they may range from mere altruism to becoming one of the very first beneficiaries of a newly developed safe and efficacious treatment.

In the specific case of pediatric research, there exists a considerable consensus that clinical research in the pediatric population should only be undertaken in so far that the research serves the interests of minors, either by generating a direct benefit for the minor research subject concerned, or by yielding an indirect benefit to a larger group of beneficiaries, such as the population of minors or the group of patients to which the minor belongs.

1.4 Risks and burdens

Research participation never comes without burdens, and most often accepting a certain degree of risk is essentially part of participating in a clinical trial. Deciding upon the acceptability of the risks and burdens inherent to research participation, however, is often a complex and difficult issue, particularly when research is conducted in a vulnerable population such as minors.

Throughout the recent history of pediatric clinical research, the ethical acceptability of research risks has been the subject of considerable debate.[13] Excluding minors from research participation altogether may be considered the most effective way to protect minors from research risks. However, the practical outcome of such a stance is devastating, because it leads minors to become therapeutic orphans.[1] Therefore, alternate ways have been sought to keep minors from unacceptable research risks. At the present time, risk thresholds often play a prominent role in the assessment of the ethical acceptability of pediatric clinical trials.[14-17] As a general rule, research in minors will increasingly be considered to be acceptable as the risks involved decrease. In addition, it is a widely supported premise that,

to a considerable extent, the benefits generated by clinical research justify the risks involved.

Several principles guide the assessment of this risk-benefit ratio. First, a principle of proportionality is used to determine whether the risks inherent to a clinical trial are deemed acceptable. The greater the benefit to a person or group of individuals the research is expected to yield, the more the risk will be considered acceptable. Second, a direct benefit to the subject concerned is preferred over a benefit to more remote beneficiaries, such as the population of minors, the group of patients to which the minor belongs, or a group of future patients. As a result, the more remote the beneficiary, the higher the risk threshold. Third, also the physical condition of research subjects relates to the acceptability of research risks. The worse the condition of a patient, the higher the risk that will be deemed acceptable. In severe conditions, such as life threatening diseases at an advanced stage, decision-makers, including ethics committees, clinicians, parents, or a minor subject will be generally prepared to accept higher risks in research participation.

1.5 Pediatric expertise of ethics committees

Before research in minor subjects can start, the research protocol must be reviewed and endorsed by the competent authority and at least one ethics committee.[v] To guarantee an adequate assessment of issues that are specifically related to the conduct of clinical research in minors, ethics committees require expertise to assess rigorously research protocols. This pediatric expertise can be achieved in various ways, such as fostering pediatric expertise within the ethics committee (e.g., by having a pediatrician among the committees members), or by consulting external expertise.

2. Regulation at the supranational level

At present, clinical research is to a considerable extent regulated at the supranational level. At the European supranational level, the European Convention on Human Rights and Biomedicine, the European Clinical Trial Directive, and the Pediatric Regulation together constitute the legal framework governing pediatric clinical trials.

2.1 European Convention on Human Rights and Biomedicine

In 1997, the European Convention was denounced by the Council of Europe. In 2005, this Convention was supplemented with an additional protocol on biomedical research. To date, the European Convention is binding upon the 14 EU Member States (and 10 countries

[v] Depending upon the EU member state in which the research is conducted, the intervention of one or several ethics committees may be required

outside the EU) that signed and ratified it, and its additional protocol is binding upon the 4 EU Member States (and 1 country outside the EU) that signed and ratified it.[vi]

The European Convention specifically addresses the issue of pediatric research in art. 17 (Box 1). Also art. 6 and 16 are of some relevance, as they provide details on the protection of persons not able to consent (be it not specifically in the setting of clinical research), and the protection of persons undergoing research (be it not specifically minors), respectively. The additional protocol on biomedical research touches the subject of pediatric research in art. 17.

The European Convention's provisions on the involvement of minors in clinical research are related to the provision of informed consent, the necessity to involve minors, the interest of the research subject and the risks and burdens involved in the study.

Box 1:
European Convention on Human Rights and Biomedicine
Article 17 – Protection of persons not able to consent to research

1. Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met:
    i. the conditions laid down in Article 16, sub-paragraphs i to iv, are fulfilled;
    ii. the results of the research have the potential to produce real and direct benefit to his or her health;
    iii. research of comparable effectiveness cannot be carried out on individuals capable of giving consent;
    iv. the necessary authorisation provided for under Article 6 has been given specifically and in writing; and
    v. the person concerned does not object.
2. Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, sub-paragraphs i, iii, iv and v above, and to the following additional conditions:
    i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
    ii. the research entails only minimal risk and minimal burden for the individual concerned.

Informed Consent

The European Convention provides in art 17,1iv that the representative of the minor must grant his or her informed consent for the enrollment of a minor subject in a clinical trial. This authorization must be provided specifically and in writing. According to the European Convention, it is not required that minor research subjects provide informed consent or

[vi] In Finland, that recently signed and ratified the European Convention, the European Convention will enter into force at 1 March 2010.

assent in addition to the proxy consent provided by the parents or another legal representative. However, the active participation of minors in decisions is hereby not precluded. Quite the reverse, the European Convention does not create any hurdles to the active participation of minors in consent discussions, and even grants minors clear decision-making powers in the form of a veto right, as art 17,1v provides that research can only be carried out if the minor research subject does not object. In addition, the European Convention provides that the opinion of minors must be taken into consideration as an increasingly important factor in relation to age and degree of maturity regarding therapeutic interventions (art. 6,2). Although this requirement is provided with regard to therapeutic interventions and is not highlighted in the section on research intervention, respect for this requirement is recommended in the research setting.

Necessity to involve minors

The European Convention endorses the principle that minors should only take part in clinical research if similar results cannot be obtained without their involvement, *i.e.* by research not involving humans (art. 16,i) or research in individuals capable of informed consent (art. 17,1iii).

Interest of the research subject

As a general rule, art. 17,1ii of the European Convention provides that research on a person who lacks the capacity to provide legally valid consent may only be undertaken if "*the results of the research have the potential to produce real and direct benefit to his or her health*". In absence of a real and direct benefit to the research subject concerned, the risks and burdens are only deemed acceptable if two additional requirements are met. First, research must aim at generating benefit to persons sharing the same age category, disease, disorder, or condition with the participating research subject (art. 17,2i). Second, research may only entail a minimal risk and minimal burden to the research subject involved (art. 17,2i).

Risks and burdens

The European Convention explicitly links the acceptability of risks and burdens to the benefit involved. In the absence of a direct benefit to the research subject, only minimal risk and minimal burden are deemed acceptable. The additional protocol clarifies the notions 'minimal risk' and 'minimal burden', as according to art. 17 of the additional protocol, a research intervention only entails minimal risk if the results of that intervention generate at most a very slight and temporary negative impact on the health of the person concerned and entails only minimal burden if it is to be expected that the discomfort to the research participants will be, at most, temporary and very slight. The explanatory report illustrates minimal risk as taking a single blood sample from a child (Explanatory Report, §111), which implies that many clinical trials, especially those with investigational medicinal products and in relatively early stage of the research, are outlawed by the European Convention.

2. 2 Clinical Trial Directive

The Clinical Trial Directive mainly aims at the harmonization of the provisions on good clinical practice and the facilitation of multicentre clinical trials across the borders of individual EU Member States. All EU Member States were bound to implement this directive into national law before the deadline of 1 May 2004. In the national implementation of the European Directive, EU Member States were free to adopt stricter provisions than those set down in the European Directive, as long as the standards of protection and time limits captured in the Clinical Trial Directive were not violated (art. 3,1). As a result, there exists considerable diversity in the national provisions on the conduct of pediatric clinical research across the EU. Nevertheless, several EU member states opted for an almost verbatim implementation of the text of the Directive.[vii] The Clinical Trial Directive addresses the specific issues of pediatric research in its article 4 (box 2).

Box 2:

Clinical Trial Directive (Directive 2001/20/EC)

Article 4 – Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate

(f) directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(g) the corresponding scientific guidelines of the Agency have been followed;

(h) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(i) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(j) the interests of the patient always prevail over those of science and society.

In addition to the provisions of the European Directive, the scientific guidelines of the European Medicines Agency (EMEA) have to be followed. In this respect, specific guidance on the implementation of the Clinical Trial Directive in pediatric research practice was provided in the guideline “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population”.[18] This guideline addresses a number of

[vii] Italy, Luxembourg, Malta, Portugal and Romania opted for a (nearly) verbatim implementation of the text of the Clinical Trial Directive.

important issues involving minors in clinical trials. First, the participation of minors in decisions on their enrollment in clinical research is addressed. In this respect, assent, a term that is not used in the European Directive, is recommended as a means to enable the participation of minors in decisions. Notwithstanding this provision, the responsibility of parents to protect the interests of their child is emphasized.

Second, the grey zone in between legal incapacity to consent and factual capacity to consent is addressed. It is acknowledged that certain minors are mature enough to provide valid consent, even when they have not reached the legal minimum age. In this respect, the guideline acknowledges that "emancipated minors" must give written consent to research participation, and that the consent of the parents or another legal representative is not required for mature minors. Notwithstanding this provision, it is emphasized that mature minors can be vulnerable, and may require additional discussions and explanations.

Like the European Convention, the Clinical Trial Directive captures specific provisions on the involvement of minors in clinical research (art. 4), in which the ethical concerns of informed consent, the necessity of involving minors, the interests of the research subject, the risks and burdens involved, and the review of research protocols are addressed.

Informed Consent

Art**.** 4a of the Clinical Trial Directive requires that consent for research participation is given by the parents or a legal representative. It is specified that consent "*must represent the presumed will of the minor, and may be revoked at any time without repercussions to the minor*". In addition, the Clinical Trial Directive serves to involve minors in decisions on research participation by stating in art. 4b that minors must receive information "*regarding the trial, the risks, and the benefits of the trial*", in accordance with their capacity of understanding and provided by staff with experience with minors. Further, art. 4c provides that the (principal) investigator must consider the explicit wish to refuse or discontinue participation formulated by a minor who is capable of assessing information and forming an opinion. In the Dutch version of the Directive, however, it is stated that the will of the minor to discontinue participation must be *respected* by the principal investigator.[19]

Necessity to involve minors

The Clinical Trial Directive provides in art. 4e that minors should not be involved in research whenever similar results can be obtained by research in competent adults or by other research methods.

Interests of the research subject

The Clinical Trial Directive requires that the research generates a direct benefit. In art. 4e, this direct benefit is defined broadly as "*some direct benefit*" that either can be an individual benefit (to the research subject) or a group benefit (to the group of patients). In case of a group benefit, no additional requirements are applicable. In addition, this article requires that research is related directly to "*a clinical condition from which the minor concerned*

suffers or be of such nature that it can only be carried out on minors". The Clinical Trial Directive explicitly guards minors and their parents against financial persuasions, as art. 4d prohibits all incentives or financial inducements to stimulate research participation, except for compensation.

Risks and burdens

In art. 4g, the Clinical Trial Directive provides that clinical trials must be designed to "*minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage*". The requirement that the degree of distress and risk threshold have to be constantly monitored, captured in the same article, demonstrates the importance of this provision, as conformity with most requirements in the Clinical Trial Directive is only assessed at a single moment in time. In addition, the well-known general principle that the interests of the patient always prevail over those of science and society is adopted in art. 4i of the Directive. Somewhat notable, this provision is subsumed in the specific provisions on clinical trials on minors.

Pediatric Expertise

According to art. 4h of the Clinical Trial Directive, ethics committees that assess studies involving minor research subjects must include a member with pediatric expertise, or gain advice about the clinical, ethical, and psychosocial problems in the field of pediatrics before deciding upon the research protocol.

2.3 Pediatric regulation

Even though the Clinical Trial Directive was a milestone in the facilitation of clinical trials, further legislative initiatives were needed to address the poor interest in developing drugs for the young. To correct the disinterest of industry in developing and marketing drugs for children, the Pediatric Regulation requires that clinical trials in minors are planned and conducted for all new products entering the market. In addition, the Pediatric Regulation offers considerable rewards for the conduct of clinical trials in minors, in the form of prolongation of market exclusivity.

In contrast to the European Convention and the European Directive, the Pediatric Regulation is entirely dedicated to clinical research in minors. In art. 2,1 of the Regulation, minors are defined as the population aged between birth and 18 years of age.

The Pediatric Regulation does not specifically address ethical issues related to the involvement of minor subjects in clinical research, but focuses on facilitation and encouragement of pediatric drug development. The regulation requires that for every request for marketing authorization, a Pediatric Investigation Plan (PIP) is negotiated early in research (art. 7). This PIP is to ensure that the necessary data to use a drug in all subsets of the pediatric population are gathered in the clinical research preceding marketing authorization. However, waivers and deferrals to this general rule are possible under certain conditions. In addition, the conduct of pediatric research is stimulated with strong

incentives, as drugs tested in children obtain an extension of market exclusivity of six months (art. 36). Also for off-patent drugs, research in minors is rewarded by means of the 'pediatric use marketing authorization' (PUMA). To organize the assessment of PIPs, waivers, and deferrals, art. 3 of the Pediatric Regulation mandated the establishment of a Pediatric Committee (PDCO), having as its main tasks the assessment of PIPs, waivers, and deferrals, and to support and advise the Agency and Commission.

3. Regulation at the national level of EU member states

At the level of EU member states, national regulation set out the conditions in which pediatric clinical research can be conducted in the territory of the nation in question. The requirements captured in the national legislation of an EU member state, however, can diverge from the requirements captured in the regulatory framework at the supranational level or be applicable supplementary to the provisions in the directive.

The analysis of domestic regulatory requirements will focus on the implementation of the Clinical Trial Directive in the national legislation of EU member states. Like the analysis of the regulation at the supranational level, the analysis of the domestic legislation of EU Member States will focus on the five major ethical issues in pediatric clinical trials that are regulated: (a) informed consent, (b) the necessity to involve minors in research to obtain relevant results, (c) the interests of minors in research participation, (d) the potential risks and burdens related to clinical trial participation, and (e) the pediatric expertise of ethics committees.

3.1 Informed Consent

Article 4 of the Clinical Trial Directive addresses the specific issue of informed consent to enroll a minor in a clinical study and sets down several requirements for the consent to enroll a minor in a clinical trial. First, proxy consent must be provided by the parents or another legal representative. This consent may be revoked at any time without negative consequences to the minor concerned, and must represent the presumed will of the minor. Second, the minor concerned must receive information regarding the trial, the risks and the benefits, appropriate to his/her capacity of understanding, and provided by staff with experience with minors. Third, the explicit dissent to start or continue research participation expressed by a minor who is capable of forming an opinion and assessing the information relevant to participation in the clinical trial, must be considered by the (principal) investigator at any time. Fourth, no incentives or financial inducements may be provided except for compensation.

Among the different domestic laws that implement the Clinical Trial Directive into the national law of individual member states, diversity exists regarding all four requirements for valid informed consent. In addition, several EU Member States specifically define age criteria or an age cut-off with regard to the decision-making capabilities of minor research subjects.

Age criteria

The Clinical Trial Directive does not specify an age cut-off for medical majority. However, as a general rule, all individuals who have not reached the age of 18 years can be regarded as minors in decisions concerning their participation in a clinical trial. Nonetheless, several EU member states define specific age criteria that deviate from this general rule. (Table 2 provides an overview of the age cut-offs that are applicable in different EU Member States). For example, in Ireland, Lithuania and the United Kingdom, all individuals who have not yet reached the age of 16 years are considered minors. Alternately, several EU Member States distinguish between two age groups, each of which is subjected to specific requirements for informed consent. The age criterion that is used to distinguish age groups varies significantly, ranging from 7 to 15 years of age. For example, in Estonia, the group of minors up to 6 years of age is differentiated from minors aged 7-17 years. In the Netherlands and Spain, the age of 12 is used as an age cut-off. The Bulgarian act differentiates between "children" (being minors up to 14 years of age) and "young persons" (being minors aged 14 to 18 years old). Also in Hungary, an age cut-off of 14 years of age is applicable. Persons under the age of 14 are considered as legally incompetent, persons aged 14 and older have a "limited competency", similar to adults that are placed under limited guardianship.[6] The Finnish act distinguishes minors up to 14 years of age from minors aged 15 and older. Also Denmark distinguishes minors under the age of 15 from minors aged 15 to 17 years old. In Poland, the age of 16 is used as an age cut-off.

Table 2:

Overview of Age Criteria in the National Laws implementing the Clinical Trials Directive

	Age cut-off	**For minors in aged younger than the age criterion:**	**Minors aged older than the age criterion:**
Bulgaria	14	consent must be provided by both parents or the legal representative	must grant their consent in addition to the consent provided by the parents or another legal guardian
Denmark	15	consent must be provided by the parents or legal representative	can in some instances consent to research participation without consent provided by a parent or another legal representative, if the ethics committee grants an exception hereto.
Estonia	7	consent must be provided by the parents or legal representative	must grant their consent in addition to the consent provided by the parents or another legal guardian
Finland	15	consent must be provided by the parents or legal representative. In the case minors who are capable of understanding the importance of the research procedure, they must provide written consent in addition to the parents	can consent for clinical research participation. The parents or another legal representative must be informed, but not consent, provided that the minor is capable of understanding the important of the research procedure, and the research is of direct benefit.
Hungary	14	consent must be provided by the parents or legal representative	must not provide consent. The consent of the parents or legal representative is sufficient.

Ireland	16	consent must be provided by the parents or legal representative	are regarded as competent adults in decisions on clinical research participation
Lithuania	16	consent must be provided by the parents or legal representative and the children's rights protection agency of a district or a city	are regarded as competent adults in decisions on clinical research participation
Netherlands	12	consent must be provided by the parents or legal representative	must grant their consent in addition to the consent provided by the parents or another legal guardian
Poland	16	consent must be provided by the parents or legal representative	must grant their consent in addition to the consent provided by the parents or another legal guardian
Spain	12	consent must be provided by the parents or legal representative	must grant their consent in addition to the consent provided by the parents or another legal guardian
United Kingdom	16	consent must be provided by the parents or legal representative	are regarded as competent adults in decisions on clinical research participation

Proxy consent representing the presumed will of the minor

The Clinical Trial Directive requires that proxy consent has been obtained from the parents or another legal representative prior to enrolling a minor subject in a clinical trial. This consent can be withdrawn at any time without detriment to the minor (e.g., by a decrease in the current level of care), and must represent the presumed will of the minor. This last requirement, however, is very confusing, as it is neither clear what constitutes the presumed will of the minor, nor how this presumed will (or violations to it) can be determined.

Within the domestic law of EU Member States, considerable variation in requirements regarding proxy consent representing the presumed will of the minor can be found. First, several member states specify who must grant informed consent. The Bulgarian act emphasizes that consent must be provided by both[viii] parents or the legal guardians of the subject. Also in France, both parents must grant their consent, except in the case that (a) the research only entails minimal risk and minimal burden without detriment to the medical treatment of the minor, (b) the research is conducted on the occasion of medical treatments, or (c) one of the parents cannot give his/her authorization within time limits compatible with the methodological requirements of the trial concerned. According to the Italian decree, the informed consent of one of the parents or a legal representative must be obtained. However, when both parents are present they both have to grant their informed consent. In Latvia, the informed consent of (at least one of) the parents or a legal representative is required. In Lithuania, informed consent must be given by both parents or another legally acceptable representative of the minor, and the children's rights protection

[viii] One parent suffices when one of the parents is unknown, deceased or deprived of parental rights or, when in the case of divorce no such rights have been assigned.

agency of a district or a city. However, when the parents of a minor are divorced, the consent of one of the parents or of the legally acceptable representative and of the district or city children's rights protection agency suffices.

Depending on the age cut-off defined in domestic legislation, the consent of a minor may be required in addition to the proxy consent granted by the parents. According to the Estonian implementation of the Clinical Trial Directive, minors aged 7 to 17 years old must grant their consent in addition to the consent of the legal representative before entering a clinical trial. In the Netherlands, minors aged at least 12 years must grant their informed consent complementary to the consent of the parents or another legal guardian, unless the minor subject cannot be deemed capable of reasonably assessing his or her interests in participating in the clinical trial. Also in Spain, minors aged twelve or older must give their consent to take part in the trial. In Bulgaria, young persons (aged 14 to 18 years old) must provide their informed consent in addition to (both) parents or the custodian. In Hungary, minors with limited competency (aged 14 and older) must not grant their informed consent in addition to the consent provided by a close relative or a legal guardian. Thus, the age cut-off used in Hungary to discern incompetent minors from minors with limited competency does not have any impact on the consent process.[6] In Finland, minors under the age of 15 years who are capable of understanding the importance of the research procedure to be carried out on them must provide written consent in addition to the proxy consent given by their guardian or legal representative. For minors aged 15 and older surrogate consent is not required, provided that the minor is capable of understanding the importance of the research procedure (taking account of the age and maturity of the minor) and the research is likely to be of direct benefit to the minor's health. Here, the written consent of the minor is sufficient, although the guardian must be informed about the participation of the minor in the clinical trial. In Denmark, the ethics committee may grant exemptions from surrogate consent for minors aged 15 and older. It is emphasized that this exemption shall be granted with due regard to the nature, risk and harmfulness of the project. The exemption of surrogate consent does not rule out the holder of the custody, as it is emphasized that the holder of the custody must receive the same information and must be involved in the decision of the minor. In Poland, minors aged 16 or older must grant written consent in addition to the consent of the parents or another legal representative, in so far that the minor concerned is capable of expressing a conscious opinion about participation in the research concerned.

The Greek law does not use a fixed age cut-off, but requires that minors who are capable of comprehending the essence of the clinical trial grant their written consent in addition to the consent of the parents or the legal representative. This is also the case in Germany, where minors who are capable of understanding the nature, significance and implications of the clinical trial and who are capable of forming a rational opinion regarding participation in the trial must grant their informed consent in addition to the proxy consent granted by the legal representative. In addition, the German law clarifies that consent must only represent the presumed will of the minor whenever such a will can be ascertained. In the Czech

implementation of the Clinical Trial Directive, it is stated that consent must be respectful to the minor's age and/or intellectual capacity.

The Austrian act requires that consent has been obtained from minor research subjects in so far the minor concerned is capable of making rational decisions and of understanding the importance, scope, and risks of the trial. This consent is complementary to the consent provided by the legal guardian. In France, minors must be consulted according to their capacity of understanding and their assent for research participation must be sought. Finally, the Estonian Act provides that proxy consent must not always be respected. For minors who have not reached the age of 7, the proxy consent to enroll the minor in a clinical study must not be adhered to by researchers if the decision of the legal representative clearly violates the interests of the child concerned. This provision however, seems completely redundant, as there are no valid reasons for involving minors in research that clearly violates their interests, even if the parents would be prepared to consent to such research. In addition, parental consent never obliges researchers to enroll a minor in a study, since there is no such thing as a generally recognized right to be in a clinical trial.

Information provided to the minor

The Clinical Trial Directive stipulates that minors must receive information according to their capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits. Obviously, this general formulation leaves much to the discretion of those implementing the provisions of the Clinical Trial Directive, including the legislators of the 27 EU member states. Member states vary considerably with regard to age criteria, the content of the information, the person providing the information and the verification of understanding.

First, several EU Member states relate requirements to provide information to the age of minor subjects. In Estonia, children aged 6 or younger must, to a reasonable extent, be informed about the clinical trial and the decisions made. In the Netherlands, minors under the age of twelve and other minors that are not capable of consenting to research participation must be told what is to happen in a way they are able to understand. According to Swedish law, minor subjects who have reached the age of 15 must be provided with information about the trial and consent to research participation in so far that they realize what their part in the research entails.

Second, several EU member states provide detailed requirements about the content of the information provided. In Germany, both minors and their legal representative should be offered a counseling session with an investigator about conditions surrounding the conduct of the clinical trial. According to the Irish statutory instrument, informed consent must be preceded by an interview with the investigator (or another member of the investigating team) in which he or she has been given the opportunity to understand the nature, objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. In Ireland and the UK, the person with parental responsibility must have been provided with a contact point where further information about the trial can be obtained

prior to granting informed consent. The Czech Decree on Good Clinical Practice specifies that the information provided to the minor must include information about possible discomfort and potential problems, be provided in writing and be specifically tailored to the level of understanding of the minor whenever possible.

Third, details on the person providing the information are given in the domestic implementation of the Clinical Trial Directive of several EU member states. In this respect, the Danish law stipulates that the information be provided by a person that is familiar with the trial and possesses the educational qualifications to communicate with minors of the age group in question. The Irish legislation requires that consent is given in consultation with the registered medical practitioner who has been treating the minor.

Finally, several EU member states require that the understanding of information is verified. In the Netherlands, the party conducting the research must ensure that the person from whom consent is requested is informed of (a) the aim, nature and duration of the research, (b) the risk of participating in the trial and of withdrawing participation prematurely, and (c) the burdens involved in research participation before the consent is granted. In addition, this information must be provided in such a way that there is no reasonable doubt that it has been understood by the recipient, and the recipient must be given sufficient time to consider the information properly and to reach a reasoned decision. According to the Slovak implementation of the Clinical Trial Directive, the investigator must verify that (a) the minor has expressed the will to participate in the trial and is aware of his/her right, (b) is capable of forming an opinion and evaluating the information provided, and (c) is aware of the right to refuse or withdraw participation at any time, without negative consequences.

Explicit Dissent

According to article 4(c) of the Clinical Trial Directive, the explicit wish of a minor to refuse participation in a clinical trial or to be withdrawn from a clinical trial is to be considered at any time during the trial by the (principal) investigator, in so far the minor concerned is capable of forming an opinion and assessing the information provided. Obviously, the obligation to 'consider' the explicit dissent of the minor is open to various interpretations. Several EU Member States, however, narrow this broad formulation.

In Belgium, the Czech Republic, Germany, France, Finland, Greece, the Netherlands, and Sweden, the explicit dissent of a minor must be considered and respected. However, the Finnish law nuances that the age and maturity of the minor must be taken into account in this matter. The Swedish law explicitly adds that the dissent of a minor must also be respected in the case that informed consent has been obtained from the minor's guardians.

The Bulgarian law requires that the expressed dissent of young persons (i.e. minors aged 14 to 18 years old) is taken into account by the (principal) investigator. However, since according to the Bulgarian law, young persons must provide their informed consent prior to research participation, the function of this provision is unclear.

No incentives other than compensation

The EU has a clear policy with regard to the payment of minor research subjects. In conformity with article 4(d) of the Clinical Trial Directive, no incentives or financial inducements except for compensation may be granted to reward research participation. This requirement is adopted (nearly) verbatim in all domestic implementations of the Clinical Trial Directive.

Latvia adds in its domestic implementation of article 4(d) of the Directive that also compensation in the event of injury or death attributable to research participation may be provided to the minor. However, such compensation cannot be regarded as an incentive, and therefore this addition is not relevant and rather confusing. Likewise, in the Slovak implementation of article 4(d) of the Clinical Trial Directive, it is stipulated that financial motives, financial or other material advantages apart from indemnification are forbidden.

3.2 Necessity to involve minors

Minors are widely regarded as a vulnerable population that deserve extensive protection against harm and abuse. Therefore, minors should not be exposed to the risks to harm and abuse that are inherent to any clinical trial, unless this is strictly required to generate relevant research results for the benefit of minor patients (cf. infra).

In article 4(e), the Clinical Trial Directive requires that the involvement of minors be absolutely necessary to validate data obtained in clinical trials on persons able to give informed consent or by other research methods, and that research in minor subjects either relates directly to a clinical condition from which the minor concerned suffers, or be of such a nature that it can only be carried out on minors.

Although, theoretically, necessity is a term that is open to various interpretations, the term appears to be understood uniformly in the European legislative landscape, as no significant variation in domestic provisions regarding the necessity of involving minors in clinical research can be found in the legislation of individual EU member states.

3.3 Interests of minor research subjects

Two provisions of the Clinical Trial Directive incorporate the requirement to serve the interests of minor research subjects. First, it is required that the clinical research generates "some direct benefit for the group of patients". The interpretation of this puzzling requirement is hampered by the many ambiguities it entails, as a direct benefit is by definition a benefit to the research subject concerned and thus not to a group of individuals, and because research subjects are not necessarily patients, and patients are not necessarily minors.[19] Unfortunately, these ambiguities are not cleared up in the domestic implementations of the Clinical Trial Directive of EU member states. Second, it is required that research either relates directly to a clinical condition from which the minor concerned suffers, or be of such nature that it can only be carried out on minors.

Several member states specify the requirements captured in the Clinical Trial Directive. In Austria, investigational medicinal products must be used in accordance with the latest state

of the art of medical science, diagnose, cure, alleviate, or prevent minors from illnesses. Likewise, the Bulgarian act stipulates that the tested medicinal product must be designed for diagnosis, treatment or prevention of diseases that is specific to children and young persons. The Czech Health Act provides that research in minors must be expected to generate preventive or therapeutic benefits for the participating subjects and generate a direct benefit for a group of patients. According to the French Public Health Code, research can only be conducted in minors when the expected benefit to the participating subjects is likely to justify the foreseeable risks. Alternately, also a benefit for other minors may justify the risk that the research entails. In Germany, medicinal products can only be tested in minors if they are intended to facilitate diagnosis or prevention of diseases in minors. In addition, the German act requires that investigational medicinal products are indicated according to the findings of medical science to save the life of the person concerned, to restore a subject's health, or to alleviate his or her suffering, unless the trial is of direct benefit to the group of patients suffering from the same disease as the subject concerned.

In Estonia, the broad and unclear requirement to generate some direct benefit for the group of patients is narrowed as, according to the Estonian act, pediatric clinical trials of investigational medicinal products must be expected to generate a direct benefit to the research subject. Also in Lithuania, it is required that the research results have the potential to produce a real and direct benefit to the health of the research subjects themselves, rather than a group of patients. In the Netherlands and Hungary, clinical research may not be conducted in minors under 18 years of age unless the research is of direct benefit to the subjects. However, the requirement to generate a direct benefit is linked to a specific risk threshold: research with negligible risks and minimal burden for the minor subject concerned may be conducted, also in the absence of a direct benefit to the research subject.

3.4 Risks and burdens

In article 4(g), the Clinical Trial Directive requires that clinical trials must be designed to minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage. In addition, the risk threshold and degree of distress must be specially defined and constantly monitored.

Several EU member states provide additional details concerning the risks and burdens involved in pediatric clinical research. In this respect, the Belgian law provides that research risks may not be disproportionate to the expected benefits. More generally, the Finnish Medical Research Act requires that the risks involved in research are limited. Likewise, the Lithuanian law requires that biomedical research does not pose risks to the health or life of vulnerable research subjects.

Germany has a more restrictive policy than the Clinical Trial Directive. The German act specifies that clinical research may only cause minimal risk and minimal burden to the minor concerned. Moreover, the German act stipulates that a research intervention only entails (i) minimal risk if this intervention will result, at most, in a very slight and temporary impairment of the minors' health, and (ii) minimal burden when it is to be expected that the

discomfort for the minor will be, at most, temporary and very slight. Also in the Netherlands, pediatric clinical research that does not generate a direct benefit to the subjects participating in the trial may not cross the thresholds for minimal risk and minimal burden. The Austrian act requires that the benefits to the subject concerned outweigh the risks involved, unless when the trial (i) aims at generating a substantial progress in scientific understanding of the condition, disease, or disorder from which the minor suffers and therefore is likely to benefit the patient or group of patients to which the minor belongs, and (ii) only entails minimal risk and minimal burden.

3.5 Pediatric expertise of Ethics Committees

The legislator has assigned research ethics committees an essential task in checking the compliance of research protocols with the ethical legal requirements captured in the Clinical Trial Directive. For the assessment of pediatric research protocols, the Clinical Trials Directive explicitly requires in art. 4(h) that ethics committees either have pediatric expertise, or take advice in clinical, ethical and psychosocial problems in the field of pediatrics.

Several EU member states provide specific requirements with regard to this pediatric expertise. In France, pediatric expertise in ethics committees is required in so far research concerns subjects aged 16 years or less, and only when the ethics committee concerned has no pediatrician among its members. In Italy, it is required that ethics committees include a pediatrician among their members. The Belgian law stipulates that Ethics committees that assess and endorse pediatric protocols must include at least two doctor-specialists in pediatrics, or take advice from two doctor-specialists in pediatrics on the clinical, ethical, and psychosocial aspects of the protocol. In Bulgaria, the consultation of external experts in pediatrics by the ethics committee is mandatory for all clinical trials in children or young persons. Likewise, in Denmark, it is required that ethics committees that assess protocols for pediatric clinical trials take advice from an expert in pediatrics. The Czech Decree Good Clinical Practice requires that ethics committees perform their supervision in at least six-monthly intervals. Ethics committees lacking experience in pediatrics must involve a specialist qualified in pediatrics for the purposes of this supervision. Four member states, Finland, Slovakia, the Netherlands, and Italy, have ethics committees that are specifically devoted to minors.[7]

Discussion

Throughout the past decades, considerable effort has been made to harmonize the legal framework governing clinical trials in the EU. Hereby, attention has been paid to the specific issues in pediatric research. Particularly the European Clinical Trial Directive is a milestone in the harmonization of good clinical practice guidelines and legal requirements for conducting clinical research in minors. As such, the European Clinical Trial Directive is an important instrument in efforts to facilitate pan-European multicentre pediatric research. Nonetheless, the harmonizing capacity of the European Clinical Trial Directive is profoundly compromised

by three factors. First, apart from the Clinical Trial Directive, also the European Convention and the Pediatric Regulation govern the conduct of pediatric clinical trials in Europe at the supranational level. This supranational legal framework in its entirety, however, contains various unclear and contradictory provisions, which complicate the implementation of this legal framework. Second, a Directive, in contrast to a European Regulation, must be implemented into domestic law by all EU Member States. As such an implementation is not necessarily a servile copy of the original text of the Directive, the implementation process may create diversity within the European legal landscape. Third, not everything in the law is arranged by law, and the legal frameworks, both at supranational and at national level, leave a lot of the interpretation and implementation of the legal frameworks to those who are actually involved in the conduct of pediatric research.

First, a comparative analysis of the three main documents of the European legal framework at the supranational level reveals that this framework lacks internal consistency. Contradictory provisions between the different documents, for example with regard to provisions on the conduct of non-beneficial research and the veto-power of minors in decisions about research participation, render it difficult to interpret and implement the European supranational legal framework. Regarding non-beneficial research, art. 17,2 of the European Convention requires that in the absence of a direct benefit to the individual research participant, a minor can only be involved in research if the study only entails minimal risks and minimal burden, while art. 4e the Clinical Trial Directive only requires ”some direct benefit’” to the research subject or a related group of beneficiaries. This indicates that the European Convention endorses a more restrictive policy than the European Directive. As a consequence, early stage drug development may be compromised in Member States that have signed and ratified the European Convention. Also in relation to the power of a minor to veto participation in clinical research, contradictory provisions exist. While art. 4c of the Clinical Trial Directive provides that the (principal) investigator must consider the explicit wish of a minor to refuse or discontinue participation (in the case of a minor that is capable of assessing information and forming an opinion), art. 17,1v of the European Convention provides that minors cannot be involved in a study whenever they object to research participation. Thus, theoretically, the European Convention grants minors more extensive decision making powers than the European Directive. In addition to these contradictory provisions, the European legal framework also contains numerous contingencies that require extensive interpretation. It is for example not clear what must be understood as an acceptable risk-benefit ratio, what it means to ‘consider’ the explicit dissent of a minor, how the capacity of minors to make decisions can be assessed, or why the Clinical Trial Directive designates minor research participants as ‘patients’ and links benefits to the ‘group of patients’.

Second, to a certain extent, the domestic implementation of the clinical trial directive works against harmonization, as Member States are free to vary the original text and stipulate additional legal requirements, provided the standards of protection and time limits captured in the European Clinical Trial Directive are not violated.

The analysis of the domestic implementation of the Clinical Trial Directive in the 27 member states of the EU presented in this article shows that the domestic implementation creates considerable legislative diversity. However, despite these variations in national provisions, few of the domestic implementations of the Clinical Trial Directive appear to be a major obstacle to pediatric clinical trials. In general, research protocols can be tailored to comply with national legal requirements of a Member State relatively easily, provided that one takes notice of the domestic provisions of an individual Member State. Nonetheless, there is still a long way to go in making all national requirements of individual EU member states accessible, due to a lack of authorized translations and easily accessible compilations of all legal requirements.

Third, not everything in the law is arranged by law. Particularly the role of individual decision makers in the interpretation and implementation of European legal frameworks can hardly be overestimated. These decision makers can be institutional bodies (for example ethics committees, or competent authorities) or persons (for example clinicians, minors and their parents or legal representatives).

As the European legal framework leaves considerable discretion in the interpretation and application of regulatory requirements individual and institutional decision-makers, the implementation of this legal framework becomes largely dependent upon the bodies and/or individuals who actually decide on the involvement of an individual minor in a clinical trial. Applying the same set of rules does not guarantee a similar interpretation or application of these rules, and therefore the discretionary freedom of decision-makers in the setting of pediatric clinical research provokes a certain diversification of the regulatory landscape. The diversity in implementation of regulatory requirements, however, entails harsher consequences than the diversity of legal provisions itself because of their practical impact. Rendering the implementation of regulation dependent upon the discretion of individuals that decide upon the accessibility and execution of a research protocol, tends to make the implementation of legal requirements a poorly intelligible process, the outcome of which often appears hard to predict.

While it is true that the European legal frameworks that govern pediatric clinical research by their nature generate a considerable diversity in their actual interpretation and implementation, this diversity need not become an enemy to be defeated. Quite the reverse, the diversity in interpretation and application of the legal frameworks governing pediatric clinical research can be regarded as a considerable asset for several reasons. First, research is not an impersonal enterprise. Taking the personal concerns of clinicians, minors and their parents seriously, however, can hardly be done in a regulatory environment that fails to tolerate a certain level of diversity. Second, research is not a universal enterprise. The demographic, institutional, economic, and cultural particularities of individual member states are relevant to the design and conduct of pediatric clinical studies. Apparently uncomplicated environmental factors, such as research infrastructure may deeply affect the conduct of pediatric research. Consequently, locality matters.

Therefore, the way forward in pediatric clinical research rather seems one of dealing with diversity than one of seeking further operational harmonization. Nonetheless, certain contradictory provisions should be rectified urgently. In particular, the contradiction in the stance towards non-beneficial research between the European Convention and the Clinical Trials Directive should be resolved. This should be feasible, because now that the Clinical Trial Directive has been governing pediatric clinical trials for more than five years, we should be able to assess whether the more tolerant approach of the Clinical Trial Directive in comparison to the European Convention has permitted unethical research conduct. To our knowledge, no incidences have been reported in this respect. Therefore, it is doubtful whether abolishing the minimal risk and minimal burden thresholds would impair ethical research conduct or decrease the level of protection of research subjects. If the minimal risk and minimal burden threshold, however, do not contribute to increased ethical standards in pediatric clinical research, they may be considered an obstacle that works against the key objective of encouraging and facilitating clinical studies in children.

Although further harmonization can solve certain issues, handling diversity will be indispensible in a landscape as diverse as the EU. Operational strategies to manage this diversity, however, remain largely unexplored to date.

Recommendations for the conduct of clinical trials in minor CF-patients

A shared responsibility

The ethical conduct of clinical research is a shared commitment of all those involved. Obviously, the approval of a research protocol is by no means a full guarantee for clinical research to be ethically sound. Therefore, all parties involved have a responsibility in assessing the acceptability and appropriateness of the research, in general, and for the subject concerned, from their own, unique perspective.

Although the European legal framework only draws explicit attention to permission in the form of protocol approval and informed consent, clinicians have an important role. They must assess whether research participation is medically recommendable to the subject concerned. When the researcher is also the patient's physician, their knowledge of the patients' medical and personal background aids greatly this assessment.

Walking the thin line

The regulations that govern pediatric clinical research in the EU address ethical issues in research participation detached from the therapeutic context in which clinical trial participation is often discussed. In practice, however, the dividing line between research and therapy is often extremely thin. Therefore, dealing with the ambiguous distinction between research and therapy is essential for good clinical practice.

While framing clinical research in the therapeutic context of the minor concerned offers unique opportunities to clarify the relevance of the proposed research for the individual

minor, integrating research in a therapeutic framework may at the same time blur the dividing line between research and therapy. Therefore, it is of key importance that research is also distinguished from therapy, even when it is discussed against a therapeutic background. In this respect, it is particularly important to communicate what the patient is to expect after the trial has been terminated.

It's all about the minor

Conducting research in minors is all about minors. Therefore, minors who are eligible research subjects should have a central position and sometimes also an active role in the consent discussion, reflecting their personal desire to take part in the decision, and their maturity and developmental stage.

Notwithstanding this central role of the minor, the main responsibilities in deciding upon the enrollment of a minor in a clinical trial are in the hands of the adults surrounding them. These are in the first place the parents or legal guardians that hold the legal capacity to grant informed consent for research participation, but also their physicians and the researchers that invite them to participate in the clinical trial. All involved should strive to move beyond their personal convictions, and aspire to decide in the interests of the minor concerned.

Validate experience

In the specific case of clinical research on CF patients, it should be taken into account that due to the chronic nature of this disorder and its impact on their lives, young CF patients may already have developed above-average decision-making skills. Therefore, they should not be underestimated in their capacity to participate. Moreover, the experience that minor patients already have and will create in the near future should be taken into account.

It should be acknowledged that throughout the years, CF patients are frequently invited to participate in studies. Clinicians should therefore guard against individual CF patients participating too frequently in clinical studies to prevent them from becoming research guinea pigs. On the other hand, inordinate enthusiasm for clinical trials may create the impression that research subjects are elected to be the first beneficiaries of novel and important medical breakthroughs. This should also be avoided.

In between the lines

The supranational and national legal frameworks that govern pediatric clinical trials set down general requirements for the conduct of studies in minor research subjects. To a large extent, the interpretation and implementation of these frameworks, however, is not arranged by law but left to the discretion of those who are directly involved in the conduct of clinical trials. Here, obviously, clinicians hold an expertise and experience that is disproportionately large in comparison to that of minors and their parents. Therefore, they have a vital role in the realization of good clinical practice.

Giving shape to poorly defined ethical and legal requirements is a complex task, that should not be reduced to the responsibility of a single individual. Therefore, it is

recommended that ethical issues in the conduct of clinical research are discussed among colleagues, and that the created expertise in dealing with these issues is shared over individual trials.

Incorporate trust

The fact that clinicians, minors, and their parents (or another legal representative) are assigned a considerable role in the interpretation and implementation of the legal framework renders the relationships between these actors of vital importance. Within these relationships, trust is essential, from the moment of recruitment to the termination of the trial, to bridge the asymmetry in knowledge, expertise, and commitment of the different parties involved.

However, despite the fundamental importance of trust in the mutual relationships between clinicians, minors, and their parents (or other legal representative), also the downside of trust must be acknowledged. Trust is not infallible, can be very naïve, and may open minor research subjects to the possibility of coercion and abuse. Therefore, it is necessary that safeguards against inordinate loyalty, deception, therapeutic misconception and other ethical digressions are incorporated in clinical practice. Rather than having outsiders bringing in such safeguards, expertise should be created both in clinicians who communicate about the trial and in minors and parents who consider enrollment into a clinical trial.

Pediatric Expertise

The ethical and legal frameworks that govern pediatric research in the EU formally require that ethics committees foster pediatric expertise, either by including a pediatrician among their members or by calling in external advice. Although it is clear that individual pediatricians are to embody this pediatric expertise (*who*), it is neither clear what such pediatric expertise entails contentwise (*what)*, nor what added value such expertise should bring to the assessment of research protocols (*why*). Therefore, both the content and the aims of pediatric expertise in pediatric research should be cleared out. Hereby, it must be acknowledged that the individual pediatricians who embody the pediatric expertise of ethics committees may lack specific knowledge on certain ethical and legal aspects of their practice, no matter how experienced they are. Therefore, it is essential that pediatricians who act as an expert in ethics committees are provided with up to date, clear and relevant research results on the ethical, legal, and social issues in pediatric clinical research practice.

Previous Publication of Results

Part of the results in this paper (analysis of legislation at the supranational level) have been previously published in: Pinxten W, Dierickx K, Nys H. Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. Eur J Pediatr 2009 Oct;168(10):1225-34.

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Chapter 3: The Belgian Law

Pinxten, W., Dierickx, K., Nys, H. (2008). The implementation of Directive 2001/20/EC into Belgian law and the specific provisions on pediatric research. European Journal of Health Law, 15(2), 153-61.

Abstract

The European Clinical Trial Directive (2001/20/EC) was implemented into the Belgian legal system by the Law of 7 may 2004 concerning experiments on the human person (LEH). Apart from implementing the European Directive, this law also broadens the scope of the Directive from interventional clinical trials to all medical experiments involving human persons.

This article offers an overview of the requirements for involving minors in medical experiments that are captured in the LEH, illustrates the process of protocol review by an ethics committee, and discusses the dissimilarities between the LEH and the European Directive.

The implementation of Directive 2001/20/EC into Belgian law

Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (further: the European Directive) was implemented in the Belgian legal system by the Law of 7 may 2004 concerning experiments on the human person (further: the LEH). Three Royal Decrees arrange the operational implementation of this law, and several circulars offer help in interpretation and practical arrangements.[i]

[i] Royal Decree of 30 June 2004 providing for implementation measures of the Law of 7 may 2004 concerning experiments on the human person with regard to clinical trials with medicinal products for human use, modified by the Royal Decree of 18 may 2006. (MB/BS 26 May 2006)

Royal Decree of 15 July 2004 establishing the retributions to be paid in the context of an application for a clinical trial or an experiment. (MB/BS 16 July 2004)

Royal Decree of 27 April 2007 providing the fees to be paid in the context of Article 30, §6 of the LEH. (MB/BS 22 May 2007)

Royal Decree of 15 July 2004 establishing the retributions to be paid in the context of an application for a clinical trial or an experiment. (MB/BS 16 July 2004)

Scope

As the title of the LEH indicates, its scope is significantly broader than that of the Directive. All medical experiments conducted on human persons, and thus not only interventional clinical trials, are covered by the LEH. Art. 2,11° of the LEH defines an experiment as:

> *'Any trial, study or investigation carried out on the human person with the aim of developing knowledge particular to the exercising of health care professions as referred to in Royal Decree No. 78 of 10 November 1967 concerning the health care professions.'*

This definition is clearly broader than the definition of a clinical trial in art. 2(a) of the European Directive.

> *'Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reaction to one or more investigational product(s) an/or to study absorption, distribution, metabolism of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety an/or efficacy'.*

Also the definition of 'human person' is more comprehensive than that of 'research subject'. While the European Directive defines a subject as *'an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control'*, (art. 2(i)) the LEH defines a human person as *'a born, living, and viable person'* (art. 2,23°). According to this definition, the LEH is not applicable in research with human material already separated from the body, embryos in vitro, or corpses. Also retrospective research is excluded from the scope of the law.

The broader scope of the LEH does not imply that all experiments on human persons are subjected to the same requirements. Several provisions are not applicable in case of non-interventional experiments or experiments not involving medicinal products. In addition, the LEH makes a distinction between commercial and non-commercial research, and addresses hereby a frequently formulated point of criticism in the appraisal of the European Directive.

Requirements for the conduct of pediatric medical experiments

Pediatric clinical trials are subjected to the general requirements valid in research in competent adults and to additional requirements specific to the involvement of minors in research. The specific provisions on the involvement of minors in research captured in the European Directive and the LEH are related to (1) the specific design of the pediatric research, (2) the approval of the protocol by an ethics committee, (3) the informed consent to enroll a minor in research, and (4) the absence of incentives or financial inducements.

Scientific design of the research

Research in minors can only be conducted if certain standards related to the design of the research project are met. First, the necessity to involve minors in a clinical trial to obtain relevant results must be demonstrated. According to both the European Directive (art. 4(e)) and the LEH (art. 7,3°), it is not permitted to conduct research in minors if comparable results can be obtained by using other research methods (e.g., laboratory research or animal models) or by conducting research in other populations capable of valid consent (e.g., competent adults), as it is required that "*the experiment must be essential to validate the data obtained in experiments on persons able to give consent or by other research methods*" (Art. 4(e) European Directive and art. 7,3° LEH). Second, it is required that research is related to the participating minor. In this respect, art. 7,2° LEH and art. 4(e) of the European Directive specify that research should either relate directly to a clinical condition from which the participating minor concerned suffers or be of such a nature that it can only be carried out on minors. Third, it is provided that research in minors must generate an added value benefiting the minor research participant or a related group of beneficiaries. In this respect, art. 7,3° LEH attempts to implement art. 4(e) of the Directive that states: "*some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; (…)*". Art. 7,3° LEH and art. 4(e) of the European Directive thus both require that research generates some direct benefit for the group of patients to which the minor research participant belongs. However, it is not clear how this requirement of a group benefit must be interpreted. Especially the expression 'group of patients' in art 7,3° LEH -adopted verbatim from art. 4(e) of the European Directive- is tangling, as it does not necessarily restrict research to participants who are at the same time patients. In the light of the explanatory memorandum of the European Directive, the notion 'group of patients' can be interpreted as the group of minors in general.[1] In addition, also the specification of a 'group benefit' as a 'direct benefit' is confusing, as the 'direct' character of a benefit implies that the beneficiary is the participating individual. Fourth, whenever a research design requires the involvement of minors in research, provisions must be made to minimize the risks and burdens involved in research participation. In this respect, art. 4(g) of the European Directive is adopted verbatim in art. 7.6° of the LEH, reading:

> *'the experiment has been designed to minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and permanently monitored.'*

In addition to this minimization of risks and burdens, art. 7.4° of the LEH provides (in accordance to art. 3,2a of the European Directive) that the risks taken by minor research participants (and the foreseeable risks according to the current state of scientific knowledge) may not be disproportionate to the anticipated benefits for that individual. It is difficult to see how this requirement can be met in the case that the experiment has only some direct

benefit for the groups of patients the participant belongs to (cf. supra) and not directly for the participating minor.

Protocol endorsement by an ethics committee

Both the European Directive and the LEH require that the research protocol is endorsed by an ethics committee before research commences. The Directive introduces three important innovations in relation to obtaining ethics approval: (a) the provision of single ethics opinion in multicentre trials, (b) the requirement of pediatric expertise in ethics committees that review protocols of pediatric studies, and (c) the determination of strict time limits for protocol review by an ethics committee.

Single opinion in multicentre trials

Art. 7 of the European Directive provides that Member States must establish a procedure for obtaining 'single opinion' in multicentre trials for that Member State. Correspondingly, the protocol of a multicentre trial now needs to be endorsed by only one ethics committee per Member State, whereas formerly approval needed to be obtained from every site. As a result, researchers are less often confronted with diverging opinions of different Ethics Committees.

In correspondence with art. 7 of the European Directive, the practical organization of the provision of single ethics opinion in multicentre research is left to the freedom of individual Member States. In this respect, the Belgian legislator opted to organize the provision of the single opinion within the existing network of ethics committees, rather than creating a new national body to perform this task. In practice, a limited number of Belgian ethics committees are authorized to provide single opinion in multicentre trials.

However, also the ethics committees that are not authorized to provide single opinion in multicentre trials take part in the review of protocols of multicentre experiments, as they report to the ethics committee providing single opinion on elements specific to a particular site These elements include the suitability of the local investigator and supporting staff, the quality and adequacy of local facilities, and the adequacy and completeness of written patient information and consent form in the local language.

Summarizing, ethics committees can act in two complementary roles when research protocols for multicentre trials are reviewed. First, if they are authorized to do so, ethics committees can act as a so called 'leading ethics committee' providing single ethics opinion in multicentre trials. Second, all ethics committees can act as a so called 'non leading ethics committee', reporting on issues specific to the site where a part of the experiment will take place.

The authorization to provide single opinion committee is granted for one year to ethics committees that acted as a non-leading committee in at least 20 multicentre research protocols or as a leading committee in at least 5 multicentre research protocols in the course of the past year. According to the most recent list published in the Belgian State

Gazette, 35 ethics committees are authorized to provide single opinion in multicentre trials, on an estimated total of 235 ethics committees in Belgium.[ii]

With at present 35 Belgian ethics committees being authorized to provide single opinion in multicentre trials, a clear trend towards centralization can be observed.[2] While in 2006 a total of 162 Belgian ethics committees[iii] assessed 3997 protocols, over 2353 of these protocols were assessed by 9 committees reviewing more than 100 protocols. This indicates a *de facto* centralization of protocol assessment to ethics committees with sufficient scientific background to provide sound advice.[2]

While it is evident that a single opinion in multicentre experiments has to be provided by a leading ethics committee, also for monocentre experiments ethics approval must be provided by a leading ethics committee. As a consequence, monocentre studies initiated at a particular site disposing of a non-leading ethics committee must be endorsed by a leading ethics committee at another site.

Pediatric expertise

The European Directive provides in art. 7(h) that ethics committees reviewing protocols of research in minors must have pediatric expertise or take advise in the clinical, ethical, and psychosocial field of pediatrics. This is implemented into Belgian law by means of art. 7.6° of the LEH, requiring Belgian Ethics committees to include at least two medical specialists in pediatrics or take advice from two medical specialists in pediatrics whenever assessing protocols of experiments involving minors.

In 2006, 4% of the studies reported to the Belgian Advisory Committee on Bioethics (n=70) were pediatric studies. No less than 10% of all research participants (n=190), however, were minors.

Time limits

The European Directive sets clear time limits for the provision of ethics opinion by the Ethics Committee reviewing the protocol. In this respect, art. 6,5 of the Directive provides that Ethics Committees must give their reasoned opinion to within 60 days from the date of receipt of a valid application. In contrast, the LEH adopts stricter time limits than those set forth in the European Directive. Art. 11 of the LEH reduces the time limit captured in the European Directive to 15 days in case of a monocentre phase I trial, and 28 days for all other experiments.[iv]

[ii] Belgian State Gazette, 11 July 2007

[iii] Ethics Committees that did not assess any research protocols in 2006 were not taken into account

[iv] In case of gene therapy or somatic cell therapy, an extension of the time limit with 30 days (+90 days) is possible. In case of xenogenetic cell therapy, no time limits are applicable. (European Directive art. 6,7)

This fast review of protocols by ethics committees makes Belgium an attractive locus for the conduct of clinical research. Today Belgium has the second highest rate of research sites for industry sponsored research per million habitants in Europe after Denmark.[3] However, it is doubtful whether such a shortened time limit is compatible with the Directive's provision that the Directive *'shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified herein'* (art. 3,1). One may wonder whether a stricter time limit is "consistent" with the timescales specified in the European Directive. While it could be argued that a stricter timing than that required by the Directive is not unlawful as such, art. 3 of the Directive mandates that the protection of research participants must be enhanced by doing so. Obviously, this is not the case. Although increased time pressure will not necessarily result in a decreased level of participant protection, it cannot be argued that it generates an extended protection of human subjects participating in medical experiments.

Informed consent

Apart from a sound research design and the endorsement of the research protocol by an ethics committee, voluntary and informed consent must be obtained before research commences.

As a general rule, consent for research participation must be granted by the subject participating in research. However, most minors cannot provide legally valid consent due to their factual limited capability of understanding information and making responsible decisions or to an age criterion captured in law. As a result, the process of obtaining informed consent in minors encompasses a number of complexities that are addressed in the European Directive and the LEH.

First, for pediatric research, art. 7.1° of the LEH provides that consent to enroll a minor in research must be granted by the parents of the minor or another legal representative. In principle, parental consent is granted by both parents. As this may be difficult to achieve in practice, however, the consent of the second parent is assumed.[v] Parental consent must represent the presumed will of the minor and may be withdrawn at any time, without repercussions to the minor. Art.7,1° LEH implements art.4 (a) of the European Directive and is formulated in exactly the same terms. It is unclear on which elements the will of an incapacitated person who never was competent before can be presumed. The consent of the parents or legal representative of the minor must be obtained in accordance to all requirements applicable to consent provided by competent adults that are captured in art. 6

[v] Art 373 of the Belgian Civil Code

of the LEH, providing that consent must be granted in writing[vi] and be preceded by specific and comprehensible written information on *'the nature, significance, objectives, implications, anticipated benefits, and risks of the experiments, the circumstances under which it is conducted, the identification and opinion of the competent ethics committee (…)*' (art. 6,§2).

Second, art. 7,1° of the LEH also explicitly provides that the minor must be involved in the exercise of the right to consent. The measure of involvement of the minors, however, is dependent on the age and degree of maturity of the minor. To enable the involvement of minors in decisions on their participation in medical experiments, the provision of appropriate information is essential. In this respect, the LEH provides that information must be geared to the minor's capacity of understanding and provided by pedagogically trained staff.

In addition, the involvement of minors is more decisive in the LEH than in the European Directive. Unlike the European Directive, the LEH provides that the explicit wish of a minor capable of forming an opinion and assessing information concerning participation to refuse participation or withdraw it must not only be considered (as provided in art.4,c of the European Directive) but also be respected: art. 7,1° of the LEH reads:

> *'The explicit wish of a minor who is capable of forming an opinion and assessing this information with regard to his participation in an experiment, to refuse participation or to be withdrawn from the experiment at any time is also considered and respected by the investigator.'*

Like the Directive, the LEH does not impose fixed age criteria for consent or as a threshold for a certain level of participation in the consent procedure.

No incentives or financial inducements

To prevent that financial profit would persuade minors and/or their parents to consent to research participation art. 4,7° of the LEH provides in accordance with art. 4(d) of the European Directive that no incentives or financial inducements except compensation are permitted.

Conclusion

The European Directive is implemented in Belgian law by the LEH. This law shows several important dissimilarities with the European Directive. First, the scope of the LEH is significantly broader than that of the Directive, as it is applicable to all experiments on human persons and thus not limited to interventional clinical trials. Second, to intensify the attractiveness of Belgium as a locus for the conduct of clinical trials, the time limits for ethics

[vi] If individuals are unable to write because of physical reasons, oral consent is valid if given in the presence of at least one witness of legal age who is independent from the sponsor and the investigator.

approval are shortened. The provision of time limits in the LEH that are shorter than those captured in European Directive, however, is not in accordance with the requirements of the European Directive, as it is clearly implausible that shortened time limits would result in a more extensive protection of minor research subject. Third, the LEH provides a more extensive involvement of minors in the informed consent process than that provided in the European Directive. While as a general rule the capacity to consent to research enrollment of a minor is granted to the parents or another legal representative of the minor, the LEH explicitly grants minors –in so far they are capable of forming an opinion and assessing information- considerable decisional power in the form of dissent. This means that the explicitly expressed refusal of (continuation of) participation by a minor who is capable of forming an opinion and assessing information must not only be considered (as provided in the European Directive) but also be respected. Like the Directive, the LEH does not impose fixed age criteria for consent or as a threshold for a certain level of participation in the consent procedure.

In the review of research protocols of experiments, 35 Belgian ethics committees are authorized to endorse the protocol. In practice, there is a clear tendency towards centralization, as a small number of ethics committees review the large majority of protocols. This tendency supports a professionalization of ethics committees, which might entail important opportunities to increase the pediatric expertise that is currently available in ethics committees.

Little is known about the practical impact of the LEH on pediatric research practice. However, it is certain that both the European Directive and the LEH leave the practical organization of many important issues (e.g., the practical involvement of minors in decisional processes, the assessment of the maturity and understanding of minors) to those in the field. Not everything is thus arranged by law. This entails both an opportunity, as medical practitioners enjoy a great deal of freedom to deal with the complexities of the case, and a challenge, as little support exists to help practitioners to translate the generally formulated requirements captured in the LEH to pediatric research practice. The practical implementation of the European Directive and its Belgian implementation in the LEH would certainly benefit from some further clarification, especially in relation to the requirement of generating ‘some direct group benefit’ in pediatric research.

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Chapter 4: Beyond regulation

Pinxten, W., Nys, H., Dierickx, K. (2008). Regulating trust in pediatric clinical trials. Medicine, health care, and philosophy, 11(4), 439-444.

Abstract

The participation of minors in clinical trials is essential to provide safe and effective medical care to children. Because few drugs have been tested in children, pediatricians are forced to prescribe medications off-label with uncertain efficacy and safety. In this article, we analyze how the enrollment of minors in clinical trials is negotiated within relationships of mutual trust between clinicians, minors, and their parents. After a brief description of the problems associated with involving minors in clinical research, we consider how existing ''relationships of trust'' can be used as a place where the concerns of research subjects can be more fully discussed and addressed. Building on the tacit recognition of trust found in The European Clinical Trials Directive we make policy recommendations that allow for clearer, more ethically informed guidelines for enrolling minors in clinical research.

Introduction: issues in involving minors in clinical research

In the course of the twentieth century, it became increasingly clear that results from laboratory research, animal experimentation and research in adults could not offer proper data to develop safe and effective drugs for use in pediatric practice. Because adults and children differ significantly in pharmacodynamics (the way a drug affects the body) and pharmacokinetics (the way the body responds to the drug), results obtained in adults cannot easily be transposed to minors. A mere recalculation of drug dosages used in adults based on a child's weight or skin surface is not reliable.[1] [2] As a consequence there are no viable alternatives to using minors in clinical trials.

In the aftermath of the Nazi experiments and a series of research scandals in the US[3] and the UK[4] minors were excluded from clinical trials. This was thought to be an efficient way to protect minors, but this strategy was eventually judged untenable. Denying minors access to clinical studies makes children 'therapeutic orphans'[5] and results in a high rate of off-label prescriptions (the prescribing of drugs not tested in children and not labeled for pediatric use).[i] As Ross[7] notes, in the absence of tested drugs every treatment becomes an experiment.

[i] It is estimated that between 7 and 60% of prescriptions in pediatric hospital wards are off-label. (6. Pandolfini C, Bonati M. A literature review on off-label drug use in children. *Eur J Pediatr* 2005;164(9):552-8.)

The involvement of minors in clinical studies, however, is a precarious enterprise. There at least three reasons for this.

1) The limited (and varied) level of maturity of children generates a plethora of ethical and legal issues.
2) The small number of pediatric patients makes research on the diseases of children commercially less interesting (and hence less likely) than research on adult diseases.[2 8 ii]
3) Clinical trials in children are practically difficult. The limited pool of children eligible and willing to participate in a clinical trial makes it difficult for physicians to recruit a sufficient number of research subjects.[12]

Negotiating the involvement of minors in clinical trials

Obtaining authorization to enroll minors in clinical research

In order to enroll minors in clinical research, researchers must gain the approval of a research ethics committee (REC) and obtain valid permission—including consent from parents and, when possible, assent from their child— to participate in a study.

Authorization to conduct research

RECs weigh three issues in evaluating research proposals that involve children: necessity, safety, and consent. Research with minors will be approved only if: (1) there is no other way to gain the needed information, (2) the risk of harm is in proportion to the expected benefits and procedures exist for reporting harm and for stopping a clinical trial if the safety of subjects is threatened, and (3) parental consent that respects the child's presumed interests is granted and children are informed and involved—to the extent possible—in the decision.

Permission to enroll individual minors

In the European normative framework, the paradigmatic research subject is a competent adult. This fact, together with age standards and other criteria for legally valid consent, make gaining valid consent from minors problematic. Given the legal impossibility of obtaining consent from minors, other methods to protect children involved in research have been developed. Most common is the use of parental consent, where the parent (or

[ii] To correct the commercial disinterest in pediatric drug development, incentives stimulating the pharmaceutical industry to conduct pediatric trials were adopted in US and EU legislation.(See: Rodriguez WJ, Roberts R, Murphy D. Current regulatory policies regarding pediatric indications and exclusivity. *J Pediatr Gastroenterol Nutr* 2003;37 Suppl 1:S40-5; Food and Drug Administration Modernization Act of 1997. http://www.fda.gov/cder/guidance/s830enr.txt (accessed: 31 July 2007); European Parliament and of the Council, Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004.)

parents) of a minor make decisions about the child's clinical trial participation. This strategy, while practical, is not completely satisfactory. Simply ignoring minors in decisions about participation in research overlooks their decisional capacity and threatens to erode the ethical standards used for research with adults.

If parental consent is to be held to the same ethical standard as informed consent provided by a competent adult, the child who is participating in research must somehow be involved in the decision-making process. This can be accomplished by means of 'assent'—the affirmative agreement of a minor to participate in research (45 CFR 46 subpart D).[13] Specification of the need for assent is a step toward more informed participation of children in research but it does not clearly define the role and position of minors in the decision to participate in research. As Olechnowicz et al.[14] observed, assent can be implemented in different ways: clinicians can opt for a ''patient-centered'' (clinicians begin by seeking the agreement of the child), a ''parent-centered'' (clinicians begin by seeking the permission of the parents), or a ''joint patient-parent approach in decision making'' (clinicians invite children and their parents to decide upon participation).

Three basic concerns when enrolling children as research subjects

Decisions to involve a minor in a clinical trial are complex. Gaining permission to enroll a child in a study is not a linear process where subjects provide their consent (or assent) at a distinguishable moment in time, i.e. when a document is signed.[15 16] Decisions to enroll a minor in a clinical trial are ''stretched out'' and require the cooperation of the multiple parties. Communication and information are essential in this procedure.[2 12] From the patient's perspective, three concerns are central.

Opportunities

First, the child and parents must be convinced that it is worthwhile to enroll in a clinical trial. The opportunities presented by research participation are diverse and may not provide benefit to the participant. Participation in research that contributes to the health and well-being of other minors, or future patients, or to the progress of science in general, may be judged worthwhile even when direct benefit to the participant is unlikely. Lacking some form of opportunity for the participant—be it direct or altruistic—the necessity of research is difficult to justify.

Feasibility

Second, the child and his or her parents must assess the feasibility of research participation. Research participation involves a considerable burden for both minors (e.g., taking drugs, blood sampling, hospitalization, follow up, physical inconveniences) and their parents (e.g., travel for study participation and follow up, drug administration, log keeping, reporting adverse events). The decision to assume these burdens must be shared by parents and their child.

Decisional freedom

Third, the involvement of minors in decisions to participate in clinical trails rests upon the decisional strategy used by the family. Parents have considerable autonomy in the way they involve their children in decision making processes. Snethen et al.[16] identify four ways minors may be involved in decisions about study participation: exclusionary decision-making (no involvement of the child), informative decision-making (the child is informed but has no decisional power), collaborative decision-making (the child is at the center of the decision-making process, but decisional power and responsibilities remain, for the most part, with the parents), and delegated decision-making (the decision is delegated to the child). The decisional strategy used varies by family type and culture.

Difficulties in addressing patient concerns in research participation

Clarity of information and decisional autonomy are essential to making good decisions about the involvement of minors in clinical trials. Unfortunately, the many contingencies and dependencies involved in research with minors make it difficult to ensure good information and unconstrained choice.

Contingencies

The setting of pediatric clinical research is rife with contingencies. The benefits and risks of participation in a clinical trial are difficult to determine resulting in ambiguous information and uncertain prognoses. Further, the provision of information is not an unbiased process. Physicians (or other clinicians) who invite minors and their parents to consider research participation provide reasons to enroll in a study, and in some cases these reasons are not health related. Simon observed that most of the altruistic discourse in enrollment discussion is provided by physicians and not by patients or parents.[17] Conflicts of interest on the part of researchers also hinder the provision of clear and reliable information. Physicians may have a personal agenda in enrolling minors in clinical trials, such as enriching their personal career, obtaining research funding, or pleasing colleagues. Bias and conflicts of interests can also influence parental decisions, especially when financial incentives are involved. Recognizing this problem, laws prohibit excessive compensation for inconvenience and hardship.

Dependency

In making the decision to participate in a clinical trial, the autonomous judgment of both minors and their parents can be impaired by relationships of dependency. In most cases minors and their parents are highly dependent on medical staff to provide and interpret the data relevant to their decision. The considerable asymmetry in information and interpretative skills between researchers and research subjects forces minors and parents to rely upon medically qualified staff to clarify the relevant data.[18]

Similarly, minors must depend on their parents to obtain authentic involvement in decisions. The decision to enroll a minor in a clinical study and the degree of the child's

involvement in the decision making process are largely left to the parents. Although the active involvement of minors in the decision is highly valued in ethics and law, the actual decision about enrollment of a minor in a clinical study occurs in the privacy of the family. Parents are trusted to make decisions on behalf of their children and to balance the interests of the minor to be enrolled and those of other family members.[19] Interventions in the privacy of the family are very rare. On occasion (depending on domestic legislation), the autonomy of parents may be limited by the obligation to respect the express dissent of a minor.

The contingencies and the unavoidable dependency associated with the research setting increase the vulnerability of both minors and their parents, forcing them to rely on others to obtain the information they need to make rational and responsible decisions.

Handling patient concerns in relationships of trust

In absence of trust, research participation is unlikely.[20] Because the concerns of parents and children are very personal and strongly related to the medical history of the minor, they are difficult to address in impersonal relationships. Hence, it is not surprising that impersonal recruitment strategies are generally unsuccessful.[21] Concerns about clinical trial participation—be they the child's or the parents'—are best situated in personal relationships, such as established relationships of trust between physicians, minor patients, and their parents. The handling of these concerns within personal relationships does not, however, relieve minors and their parents from the challenging task of deciding who and what to trust.

Trustworthiness

Trustworthiness refers to the truthful, competent, sincere, and honest character of the trustee.[22] When clinicians, minors, and their parents negotiate the participation of a minor in a clinical trial, the interests of the child must be reconciled with the opportunities and hardship involved. In this process, minors and their parents are bound to rely on clinicians to close the gap in expertise and knowledge. Because misconception, manipulation, deception, and coercion cannot be precluded in the provision of information, the trustworthiness of the clinician who invites the child to participate is of great importance. Trust is required for minors and their parents to rely on the future and contingent actions of researchers.[22] In addition to trust in the person of the researcher, a child and his or her parents must trust the aims and methods of the proposed research.

Just as trust cannot be ignored, there is no suitable substitute for trust. O'Neill[23] argues that mere transparency, autonomy, or accountability—although each is of great value—cannot compensate for trust. Therefore, and even in the face of its possible abuse, we must find a way to promote and enhance trust.

Trust issues in the European clinical trials directive

Entrusting issues

Trust is, as we have shown, essential to address the major concerns of minors and their parents with regard to clinical trial participation. While ''trust'' is not an explicit part of the regulations governing the use of minors in research, by assigning tasks and responsibilities to various trustees, European legislation implicitly recognizes the importance of trust. More specifically, the Clinical Trials Directive of the European Commission and the European Parliament (2001/20/EC, further: the Directive)[24] serves to organize and distribute trust among specific persons and institutional bodies.

The Directive is not explicit in this regard. Rather, the legislation simply formulates general principles and leaves the interpretation of these principles to those charged with implementation. The provision of information and the active involvement of minors in the decision making process, are, for example, left to the field of pediatric research practice, as is the determination of what counts as successful accomplishment of these tasks. Clinicians, minors, and their parents must determine what constitutes appropriate information or suitable involvement of minors in decision making. Other decisions, however, are explicitly removed from pediatric researchers and given to external bodies, such as the national legislator, the EMEA (European Medicines Agency), or Research Ethics Committees.

European concerns

At the European level, the main concern is to promote the European Union as a competitive research environment. The interventions intended to make Europe an attractive destination for research include the simplification of REC-approval in multi-centre clinical trials, the introduction of strict time limits for the provision of REC approval, and the provision of harmonized REC- procedures by means of detailed guidance issued by EMEA.

The desire to be competitive, however, does not overrule the need to protect research subjects. In this respect, the Directive explicitly states that the interests of the research subject always prevail over those of science and society. The Directive specifies a wide range of subject protection measures, calling on several existing ethical and legal documents—including the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice,[25] the Declaration of Helsinki, and the Convention on Human Rights and Biomedicine[26]—to provide a general framework for these measures. However, the interpretation, implementation, and control of the issues related to research subject protection (both adults and children) are entrusted to the individual Member States and/or those in the field of research.

Public concerns

Two major tasks in arranging responsible scientific progress—the assessment of the necessity of research and the safety of clinical trials—are given to the individual Member States and handled by a Research Ethics Committee and/or the competent authority. The

Directive specifies that in the assessment of pediatric research, RECs must call on pediatric expertise or get other expert advice on the clinical, ethical, and psychosocial problems associated with the participation of children in research.

With regard to the necessity of a clinical trial, RECs must assess whether the clinical trial generates some direct benefit to the group of patients and whether research is essential and cannot be done using adults or other research methods. RECs also must assess the safety of the clinical trials and determine whether the expected risks are proportionate to the anticipated benefits, whether the staff conducting the research is qualified, whether written information for informed consent is of sufficient quality, whether the provisions for indemnity or compensation are satisfactory, and whether pain, fear, discomfort, and other risks are accurately minimized. RECs are also charged with creating a system to monitor serious adverse reactions.

Private concerns

The Directive provides only general guidelines governing the opportunity to be in research, the decisional freedom of minor subjects and parents, and the feasibility of participation. This means that researchers, minors, and parents must negotiate concerns about these issues within the general framework set down in European law. There is wisdom in this lack of regulation. The fact that these ‘‘private concerns’’ are left to the field of pediatric research allows them to be addressed within the existing relationships of trust between researchers, minors, and their parents. Overregulation would move these concerns from the relationships of trust to an inflexible bureaucracy.

The way forward

At first glance, the European Clinical Trials Directive seems to provide a comprehensive and complete framework for protecting research subjects. The interests of the European Union are dealt with served at the European level, public interests are given to the domestic sphere of competent authorities and Research Ethics Committees, and private concerns of clinicians, minors, and their parents are left to pediatric research practice to be worked out within relationships of trust. There are, however, important gaps in the system.

The problems associated with the contingencies and dependencies found in clinical research with children are poorly addressed in the Directive.

Discussion: coping with the downside of trust

To some, the act of trusting can seem naïve, opening research subjects to the possibility of abuse. What can we do when trust fails? How can we deal with the deception, coercion, or harm associated with the contingencies and dependencies involved in research participation? In order to improve the process of recruiting, informing, and including minors in clinical trials we must acknowledge the downside of trust.

Informed consent, assent, and dissent

The doctrine of informed consent plays an important function in the pediatric setting by specifying liability and confirming (symbolically) enrollment in a clinical trial. On the other hand, informed consent in pediatric clinical trials fails to address several concerns of minors and their parents in the decisional process. This is especially true in decisions where parents have no choice e.g., when the only medical interventions for their child's illness are experimental.[27] The problems of informed consent for pediatric research are not relieved by the use of assent. Because minors are not capable of settling liability issues, the only added value of assent is as a formal affirmation of willingness to participate in research. While this affirmation is important (it provides tangible evidence of the commitment of the minor), the signature on the assent document puts too much weight on the role of formal documentation.

Focus on the documentary evidence of consent and assent turns ethical standards into bureaucratic ones and distracts from important and ongoing relationships of trust. It is in these relationships where the true concerns of research participation are addressed. We believe that the best way to involve minors in decisions about research participation is to embed those decisions in an ongoing patient–physician relationship characterized by mutual trust. It is in these relationships that children and parents can freely express their concerns about the research and about the decisional capacity of the child subject.

Recruitment

Impersonal recruitment strategies, including recruitment by an independent person who does not know the details of a child's medical condition and history, do not work.[21] Not only do they yield few participants, they have little potential to address the concerns of minors and parents contemplating enrollment in a clinical study.

As with consent/assent, relationships of trust are a good locus to negotiate the inclusion of a minor in a clinical trial.

There are, however, important caveats about this recruitment strategy: (a) even within relationships of trust there is the potential for bias and (b) not all physicians are able to address the concerns of minors and parents about clinical trial participation. Minors and parents must be empowered to identify and discuss their concerns, and physicians must be instructed in responding to the issues of pediatric research.

Empowering minors and their parents

In our opinion, the best way to overcome the problems associated with using existing relationships of trust as the location of informed consent discussions is the appointment of an independent counselor. This counselor will inform minors and parents about their fundamental rights as research participants, help them to identify and discuss their concerns, and make them aware of the potential biases of the physicians who are recruiting them for a clinical study. The counselor must be able to explain the consent documents, and aspects of the clinical trial, and to answer questions that minors and parents may be

reluctant to ask the physician. The counselor must have sufficient expertise to assess the information provided to minors and their parents and to examine whether the concerns of minors and their parents have been adequately addressed. The availability of an independent counselor—one who is capable of providing advice and judging whether minors and their parents were correctly invited and well informed—will strengthen the trustworthiness of research and help minors and their parents to decide where to place their trust.[23]

Creating expertise in physicians

The delicate task of informing minors and their parents about why it would be good for a minor to participate in research requires: (1) knowing the child and his or her medical background well, (2) being aware of the child's ability to cope with the hardship of participation in a clinical trial, and (3) being familiar with decisional styles characteristic for a family. Physicians who know the family well are well positioned to do this. Dealing with the concerns of minors and their parents about participation in a clinical trial, however, requires more than knowledge of the medical and social situation of the child.

In order to promote the ethical inclusion of minors in clinical trials, physicians must enhance their communication and information skills. Although studies suggest that few physicians actively ask for such measures,[15] we are convinced that such a measure is a necessary step for the implementation of a normative framework that addresses the true concerns minors and parents.

Laws, directives, and guidelines provide the framework for the protection of the subjects—both adults and children—of medical research. But these ''paper rules'' must be affirmed by the ''real rules'' that govern what occurs in research practice. With regard to pediatric clinical research, the real rules of research—and real protections for minors—are found in relationships of trust between physician- researchers, children, and parents. These relationships have a high yet under-employed potential to address subjects' concerns about research participation. By creating know- how in physicians and empowering minors and their parents, relationships of trust can become the place where patient concerns are effectively discussed and addressed, where minors truly can be involved in decisions, and where ethical and legal standards are effectively implemented in pediatric research practice.

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Part II

In search of normative orientation

Chapter 5: Essentials for the ethical and regulatory agenda

Pinxten, W., Nys, H., Dierickx, K. (2010). Frontline ethical issues in pediatric clinical research. Ethical and regulatory aspects of seven current bottlenecks in pediatric clinical research. European Journal of Pedatrics 169(12),1541-8.

Abstract

In the course of the past decades, considerable effort has been expended on the ethical guidance and legal regulation of pediatric clinical trials in Europe. Nonetheless, the conduct of clinical research in the population of minors continues to generate myriad ethical and regulatory issues. This paper explores seven bottlenecks in the ethical guidance and legal regulation that currently govern pediatric clinical research: (1) the integration of research in therapy, (2) the education of clinicians, (3) the empowerment of families, (4) the harmonization of protocol review, (5) the assessment non-clinical research objectives, (6) the control of placebo use, and (7) the provision of fair incentives for pediatric research conduct. For all of these issues, a clear view on the way forward is largely lacking, either because these issues have not been discussed in depth to date or because the existing debates have failed to generate a generally supported consensus.

Introduction

In the course of the past decades, considerable effort has been expended on the ethical guidance and legal regulation of pediatric clinical trials in Europe. Nonetheless, the conduct of clinical research in the population of minors continues to generate myriad ethical and regulatory issues.

This paper explores seven bottlenecks in the ethical guidance and legal regulation that are currently governing pediatric clinical research: (1) the integration of research in therapy, (2) the education of clinicians, (3) the empowerment of families, (4) the harmonization of protocol review, (5) the assessment of non-clinical research objectives, (6) the control of placebo use, and (7) the provision of fair incentives for pediatric research conduct. For all of these issues, a clear view on the way forward is largely lacking, either because these issues have not been discussed in depth to date or because the existing debates have failed to generate a generally supported consensus.

Most of the issues that are explored in this paper are not exclusively associated with pediatric research; they also apply to a certain extent to research in other populations. Nonetheless, this collection of issues is particularly relevant from the viewpoint of pediatric clinical research, as it provides an overview of the major ethical concerns in current pediatric research practice.

Integrating research in therapy

A first challenge to the current ethical and regulatory framework guiding pediatric clinical trials is to clarify the ambiguous distinction between research and therapy. Traditionally, clinical research is explicitly distinguished from therapy, discerning therapeutic interventions with validated medicines from research interventions.[1 2] Because the therapeutic nature of research always remains ambiguous and uncertain—even when research is expected to yield therapeutic benefits—research interventions are associated with increased uncertainty and risks. Therefore, in a sense, research starts where therapy ends. In pediatrics, however, a rigid distinction between research and therapy is untenable.

Due to stringent lack of medicines that are labeled for pediatric use, a large part of the medicines used in pediatric practice are prescribed off-label.[3-7] As a consequence, the dividing line between research and therapy may at times be very thin, as both the off-label prescription of drugs and the conduct of clinical trials introduce the experimental use of medicines in pediatric practice. Therefore, research interventions in a clinical trial do not necessarily subject the minor subject to additional risks or to a more contingent therapeutic course than the (off-label) standard of care.[8] Quite the reverse, participating in a clinical trial may entail several advantages in comparison with being treated off-label. First, research interventions in clinical trials are administered in a controlled fashion, which includes a close follow-up of adverse reactions and adverse events. Second, European law requires that the sponsor's insurance or indemnity guarantees an adequate compensation in case research subjects would be harmed while participating in the trial.[9] Third, research is governed by ethical and regulatory requirements that are to positively affect the quality of research (e.g., the European Clinical Trial Directive specifically addresses research in minors).[9] Finally, the development of safe and efficacious drugs for those in need of a (better) treatment is intrinsically valuable.

Thus, in pediatrics, research not necessarily starts where therapy ends and, by contrast, may present itself as a therapeutic option. Therefore, the rigid distinction between research and therapy should be abandoned in the pediatric setting, and invitations to enroll subjects in a pediatric clinical trial should be framed in the therapeutic context of the individual minor concerned.

As the recruitment of minor research subjects is a highly personal enterprise,[10] minors and their parents want to know why it would be worthwhile for the individual subject to participate in a trial, rather than merely being informed about the trial, the risks and the benefits according to the specificities described in the study protocol. Discussing clinical trials against the background of a patient's course of disease, medical history, current treatment, and prognosis creates opportunities to provide correct and personally relevant information on the risks, burdens, and benefits related to clinical trial participation. As a consequence, framing research in the therapeutic context of individual patients is likely to serve clinicians, minors, and their parents in making honest, realistic, and well-informed commitments with regard to the clinical trial participation.

Notwithstanding these significant opportunities, the integration of research in the therapeutic context also has important drawbacks. The asymmetry in expertise between clinicians and minors and their parents and the contingency of both therapy and research must render one vigilant with regard to biased information, conflicts of interest, therapeutic misconception, dependency, or uncritical loyalty of minors and their parents toward their physicians.[11-16] Nonetheless, none of these threats need to be insuperable, provided that appropriate safeguards are set up. To a large extent, this can be achieved through the education of clinicians and the empowerment of families deciding upon research participation (cf. infra).

Educating clinicians

Many of the ample, complex and diverse tasks in the implementation of the ethical and legal frameworks governing pediatric clinical research are left to the clinicians who conduct clinical research in minor subjects.[17] To permit these clinicians to acquit themselves from their tasks successfully, they are granted considerable latitude in interpreting and implementing the applicable ethical and regulatory requirements. This discretion in the interpretation and implementation of essential aspects of good clinical practice (GCP), however, is a double-edged sword. On the one hand, it facilitates the successful implementation of ethical and regulatory requirements for several reasons. First, it is respectful of the established routine of making medical decisions on a case-by-case basis. Second, granting both latitude and responsibility to clinicians counters the sometimes serious workability problems that are characteristic to top–down implementation strategies. Third, this approach thwarts overregulation and is therefore likely to prevent that ethics are transformed into a meaningless bureaucratic burden.[18] On the other hand, there are also important drawbacks to the discretion of clinicians. A lack of communication skills, poor knowledge of the relevant ethical and regulatory requirements, conflicts of interest, and time constraints all can be serious hurdles to a successful implementation of GCP standards.[19-22] Therefore, providing support to clinicians who implement GCP standards on the floor is essential for guarding the quality of GCP.

To prevent that the quality of the implementation of ethical and legal requirements depends upon the capacities, skills and experience that individual clinicians developed fortuitously, proper education in medical ethics and law is essential. By preference, training in ethics and law exceeds theoretical courses in the curriculum of medical education and also entails the coaching of junior researchers by experienced researchers and by experts in medical ethics and health law. Just like medical students who study medicine in the classroom and become doctors as they walk the hospital wards,[23] also the capacities required to implement GCP standards in pediatric research practice should be nurtured both in the classroom and on the floor.

Empowering families

Like clinicians, also families face complex and diverse tasks with regard to clinical trial participation. First of all, families have to deal with invitations to enroll a minor family member in a clinical trial. Due to several factors, this may be a complex and confusing task. For example, invitations to enroll a minor in a clinical trial may come unexpected and prompt minors and their parents to deal with their emotions, assess their interests, and decide upon clinical trial participation, often in complete absence of relevant decision-making experience. They may feel like anything in between being elected as the first beneficiaries of exclusive and marvelous novel technologies that are not yet available on the market and being exploited as a guinea pig.[24 25] In addition, decisions on study participation are often subjected to serious time constraints, as participation may have to start very shortly after a new diagnosis, a particular event (e.g., a crisis), or a certain stage in the course of a disease.

Second, minors and their parents face the difficult task of making decisions based on difficult, voluminous, and contingent information. Obviously, feeling overloaded with information that is too complex to comprehend may render it difficult or even impossible for minors and their parents to make a well-considered decision and even tempt them to leave the decision to someone else altogether.[26] Studies have pointed out that it is difficult to understand and remember the contingencies intrinsic to pediatric clinical trials, such as the concept of randomization.[27-31] Furthermore, the distinction between research and therapy is often hard to grasp, as is suggested by the widespread phenomenon of "therapeutic misconception",[11 12 15 16] which indicates that research interventions may be attributed therapeutic qualities erroneously. Finally, also the risks inherent to clinical trials may confuse minors and their parents, as consenting to procedures that may negatively affect the health and welfare of a minor can be disturbing.

Third, families have an extensive discretion in the distribution of decisional power and responsibilities among the minor and his parents. As most minors cannot provide legally valid informed consent, they are represented by their parents in informed consent discussions. However, this involvement of parents as proxy decision maker does not preclude minors from active involvement in the decision. Quite the reverse, the ethical principle of respect for persons requires that minors are involved in the decision-making process, to the extent possible and in function of their age and maturity.[32-35] Research pointed out that families handle different strategies to distribute decisional power among their members.[36] As a consequence, decision-making is first and foremost a family affair.

Fourth, families must weigh the enrollment of a child in a trial to other family concerns. In this respect, the practical burden of having a child participating in a clinical trial (e.g., administrative requirements, additional hospital visits) may be hard to reconcile with the interests of other family members, as all parents are limited in time and abilities.[37]

Fifth, the considerable differentiation in expertise, tasks, and responsibilities among minors, their parents, and clinicians constitutes asymmetric relationships that complicate

decisions on clinical trial participation.[14] This asymmetry creates a dependency of minors and their parents upon each other and upon clinicians to provide, explain, and frame information, which raises serious ethical concerns about conflicts of interests, uncritical loyalty towards physicians, and information bias. Nonetheless, all of these issues can be addressed adequately and need not be a hurdle to the establishment of relationships of mutual trust between all individuals involved in the decision.[17 38]

It would be unreasonable to expect from family members to just own the skills and know-how that are required to make well-considered decisions on the enrollment of a minor family member in a clinical trial. However, at present, easily accessible support for minors and their parents in deciding on research participation is largely lacking. Therefore, efforts should be made to employ the vast and unexplored potential of empowering families for the advancement of ethical conduct in pediatric clinical research.

Streamlining protocol review

Competent authorities and ethics committees have a leading role in guiding sponsors, clinicians, minors, and their parents through the complex landscape of GCP in pediatric research conduct. To procure a safe and successful journey for all involved, competent authorities and ethics committees endeavor to identify and address various foreseeable obstacles to GCP in the protocols that they review.

However valuable the efforts of competent authorities and ethics committees in embedding GCP in pediatric research are, the protocol review they perform is often experienced as problematic by sponsors and investigators for several reasons. First, applications for protocol review most often generate a considerable administrative burden.[39-43] Second, the diversity of the legal requirements protocols that have to be complied with is often experienced as a hurdle.[44] Depending on the geographical location where the research is conducted, compliance with specific domestic regulation may be required.[45] This may result in a differentiation of the study protocol, as each review may induce specific changes or amendments to the protocol, which may complicate the central coordination of the study. Third, multiple assessments of the same research protocol, which for example occurs in the case of multinational trials, may result in diverging or even contradictory assessment outcomes.[45-48] This renders the process of protocol review unpredictable, as the same protocol may be accepted in one country and rejected in another, or even be accepted at one site and rejected at another within the same country.[49] The consequences of these variations in outcome for sponsors and investigators are harsh, as the timing of clinical trials may get disrupted seriously, and delays at individual sites are likely to drive up the costs of a clinical trial. For investigator-initiated trials with a clearly marked start and end, delays in getting ethics approval in all trial sites may put success of the entire project at risk.[50]

The unpredictable outcome of protocol review by competent authorities and ethics committees is a recurrent source of frustration. Ultimately, the considerable variations in

outcome may create even a wrongful impression of arbitrariness to sponsors and researchers who organize multicenter pediatric clinical trials. However, protocol review cannot be streamlined easily, as the large number of ethics committees works against a truly harmonized approach. Reducing the number of committees involved, however, is not an acceptable quick fix for this issue, as the assessment of specific issues related to the site where the research is conducted (e.g., a local hospital or research team) is vital in the review of research protocols. Location thus matters, and to date, local concerns tend to overrule the quest for a harmonized and unified protocol review. In addition, a far going harmonization of the ethical criteria for protocol review simply is no panacea because applying the same set of criteria by no means guarantees a standardized and predictable outcome. Obviously, different individuals or committees may decide differently, even when they use the same criteria.

In the absence of a complete harmonization of regulatory requirements, however, important efforts to streamline protocol review can still be made. In this respect, among many other things, increasing the transparency of protocol review, ameliorating the direct communication between research sponsors and protocol reviewers, and having members of reviewing bodies sharing expertise across national borders all could contribute to this process.

Non-clinical research objectives

Biomedicine is a rapidly developing enterprise that is capable of silently outgrowing the ethical and regulatory frameworks that guide scientific innovations through our complex society. Sometimes, scientific breakthroughs significantly alter the objectives and outcomes of medical interventions, calling bioethics and health regulation to enquire new issues, or even to move to a new paradigm. A contemporary, paradigmatic illustration of this process can be found in pediatric magnetic resonance imaging (fMRI) research.

Apart from the obvious clinical interest in pediatric fMRI, like the support of brain surgery or the diagnosis of conditions and diseases, the technique of fMRI has a great potential for developing non-clinical applications, for example in the field of jurisprudence (e.g., lie detection, moral decision making, accountability), education (e.g., memory enhancement), or marketing (e.g., consumer brand attachment, persuasion), several of which have been registered already.[51]

Fostering the pursuit of non-clinical objectives within pediatric clinical research practice challenges the established procedures of protocol review by ethics committees and generates profound ethical questions regarding the acceptability of involving minors in clinical research, the assessment of research risks, the fair compensation of research participation, and research sponsorship.[52]

First, hosting the development of non-clinical applications of medical technologies in clinical trials threatens to erode the basic grounds for involving human subjects in clinical studies because such research no longer ultimately aims at improving the health or quality

of life of minors. Even worse, there is no single guarantee that such studies serve the interests of minors in any way at all. Therefore, the acceptability of such research is highly questionable.

Second, it is questionable whether research risks, even the slightest, can be justified if research merely is conducted for the realization of research objectives in which children have no intrinsic interest. However, in the current system of protocol assessment, most protocols of pediatric fMRI research will smoothly comply with even the lowest risk threshold due to the very low risks and noninvasive character of the research interventions concerned. In addition, risk assessments tend to largely ignore the considerable socioeconomical risks of pediatric fMRI research.[51]

Third, the resistiveness to financial incentives to reward research loses its significance when pediatric research pursues non-clinical objectives because the development of non-clinical applications of medical technologies is essentially a commercial, non-health-related enterprise in which restrictions on compensation no longer seem to be rational.

Fourth, hosting the development of non-clinical applications of medical technologies within pediatric clinical research is likely to attract sponsors from outside the biomedical setting. Such an introduction of new sponsors generates specific ethical and regulatory issues, as new players in the field may lack familiarity with clinical research and expertise in dealing with research subjects in an ethical way.[51]

To date, many questions with regard to the objectives of pediatric clinical research remain unanswered. Is clinical research the setting were non-clinical applications of medical technologies should be developed? Is the involvement of minor subjects in clinical research supporting the development of non-clinical objectives ethically acceptable? Can the technology transfer from medicine to broader society be guided and regulated? Should the ethics committees that review research protocols act as a gatekeeper that guides the technology transfer from biomedicine to society? Obviously, these questions need to be addressed urgently.

Controlled placebo use

A radical dissimilarity between experimental therapy and clinical research is that research is controlled. Among other things, this control entails that, within a trial, the safety and efficacy of investigational interventions are measured against a comparator. In the case of drug trials, the comparator may be another medicinal product, a different dose of the same medicinal product, another combination of medicines than the tested combination of medicines, or a placebo.

Double-blind randomized controlled trials (RCT) are widely regarded as the golden standard in testing treatment efficacy.[53] Particularly, RCTs in which the control is a placebo are a highly efficient way to test the efficacy of medicinal products. However, there is something profoundly ambiguous about using placebos as a control in pediatric RCTs.

On the one hand, placebo controlled trials offer the considerable advantage that the sample size of research subjects that is required to generate relevant results can be downsized significantly in comparison with other research designs.[54 55] This advantage is of great value, as various scientific, practical, and ethical considerations argue a case for small sample sizes. Scientifically, placebo-controlled RCTs generate the most reliable data, as in absence of placebo-controlled studies investigational medicinal products that are no more effective than a placebo might gain approval based on the data derived from active controlled equivalence investigations. In addition, it may be hard to find an acceptable active comparator in pediatric clinical trials because, in many cases, the standard of care in pediatric practice is off-label and therefore cannot always be used as a comparator. Practically, it must be acknowledged that, by nature, the pediatric population is quite small, which renders the recruitment of a sample of minor research subjects that is large enough to generate relevant data difficult.[56 57] As a result, complex and expensive multicentre or multinational trials may be the only way to conduct a scientifically sound clinical trial, and decreasing the sample size of research subjects in pediatric clinical trials generates a substantial practical advantage. Ethically, at least two principles argue in favor of downsizing the sample of research subjects in pediatric clinical trials. First, the principle that children should only be involved in clinical research, in so far that there are no alternatives to generate the required data, is widely alleged in ethical guidelines and legal regulations. This premise is often interpreted as a prohibition to conduct research in minors whenever relevant data can also be obtained by laboratory research, animal trials, or research in competent adults, rather than an obligation to minimize sample sizes. Nonetheless, endeavors to minimize the sample size of pediatric clinical trials would certainly square with this ethical principle, and involving more minors than necessary in burdensome or risky clinical trials will be especially hard to justify ethically. Second, there exists a general consensus that the risks in pediatric clinical research should be minimized. In this respect, it has been demonstrated that using a placebo may decrease the incidence of harm in pediatric clinical trials and, as a consequence, decrease the risk of harm. Even though the relative risk of enduring a therapeutic disadvantage from research participation is higher in placebo-controlled trials than in trials with an active comparator, the absolute number of disadvantaged research participants may still be smaller in placebo- controlled trials because due to the decreased sample size, fewer subjects are at risk.[58]

Regardless of the scientific, practical, and ethical advantages, placebo-controlled RCTs are often ethically contested for several reasons. First, the concept of randomization is proven to be hard to understand for the subjects participating in research and their proxy decision makers.[27-31] Second, desperate patients who face all validated treatment options being exhausted may be reluctant to participate in placebo-controlled RCTs, as they are reluctant to settle with anything other than the active substance. Third, placebo use may result in a wash out of the current treatment, resulting in additional risks, a decreased level of care, and a violation of the principle of equipoise, which requires that all arms of a study are reasonably believed to have a comparable chance of being the “better arm”.

To date, the ethical controversy surrounding placebo- controlled trials in minor subjects has not been cleared out, and the considerable advantages and disadvantages of placebo use in pediatric RCTs render it particularly hard to take an appropriate ethical stance. Polarizing the discussion as an ethics versus science discussion, however, is not an appropriate way forward, as banning placebo use in pediatric clinical research practice altogether is not a realistic option. By contrast, suggesting that placebo use in pediatric trials is to be eliminated obscures the devastating impact of banning placebo on the quantity and quality of pediatric trials, pushing minors back into "therapeutic orphanage".[59] Nonetheless, it must be acknowledged that placebo-controlled trials are not always the best, not to say the only way to conduct clinical trials in minors. Therefore, prudence is ethically imperative, since the high efficiency of placebo-controlled RCTs may bias researchers and sponsors to opt for this strategy. The true challenge in front of us is thus to find a feasible way to control the use of placebo in pediatric clinical trials. In our opinion, this should not be realized by defining a "golden rule" for the use of placebo in pediatric research, as such rule would ignore the complexities and needs of individual cases. Rather, efforts should be made to inform and optimize the assessment of placebo use on a case-by-case basis.

Rewarding research

Due to several constraints, research in minors is by and large commercially less attractive than research in competent adults. First, the small size of the pediatric public generates a geographical spread of eligible minor research subjects, often rendering recruitment and follow-up difficult and costly. In addition, due to the small size of the group of minors, the market for drugs for pediatric use is relatively small. Jointly, the small market and the high development costs of medicines for the young tend to tumble the profits involved in pediatric drug development.

Second, the pediatric population is very heterogeneous, as is clearly illustrated by the well-known age classification of International Conference on Harmonization guideline E11[60] dividing minors in the subsets of preterm newborn infants, term newborn infants (0–27 days), infants and toddlers (28 days to 23 months), children (2–11 years), and adolescents (12 to 16–18 years, depending on the region). Because subjects categorized in different subsets of the pediatric population tend to differ significantly in body composition and functioning, sometimes, specific research needs exist for different subgroups of minors. Obviously, handling this heterogeneity comes at a price and drives up the costs of pediatric research.

Third, because the dosage prescribed is often determinate for the retail price, the small dosages that are typical for many pediatric drug prescriptions weigh on profits involved in pediatric drug development.

The high costs and relatively low yields in pediatric clinical research make that a fair return on investment is often highly uncertain.[61] Therefore, the pharmaceutical industry is not likely to show much enthusiasm in developing drugs for the young. To counter this

commercial disinterest, regulatory efforts have been made in the USA and the EU, granting companies that invest in the development of drugs for pediatric use a considerable reward in the form of an extension of the market exclusivity of the drug in question for example, the FDA modernization act in the USA,[62] and the pediatric regulation in the EU.[63] However, despite this incentive, the financial outcome of pediatric drug development remains highly variable.[61]

For some medicinal products, the incentives will hardly, or even not at all, cover the costs of the trial.[61] In this case, the incentive does not suffice to win pharmaceutical companies over to test a drug in minors. For other medicinal products, peculiarly for blockbuster drugs, the profits involved in testing the substance in minors can be very lucrative as a result of the provided incentive, prompting the industry to test these drugs in minors, regardless of any priorities in pediatric drug development. Therefore, it is questionable whether such rewards are rational at all.

The outcome of the extended market exclusivity as an incentive for developing drugs for the young is thus as uncertain as troublesome and may generate numerous ethical issues. We suggest that three issues are addressed in this regard.

First, this type of incentive turns science-driven priorities into market-driven priorities, which may only respond accidentally to the real needs of minor patients. As a result, minors participating in clinical research rather serve the interests of the industry than their own medical interests or those of related beneficiaries.

Second, extending market exclusivity as a reward for conducting pediatric research regardless of the outcome of the investigation—as is the case in the EU—it is likely to negatively affect the quality of clinical research. If the conduct of pediatric research as such becomes more important than the successful pursuit of specific research objectives, “the cheaper, the better” tends to become a basic principle of pediatric drug development. Conversely, making the outcome of pediatric trials a requirement for obtaining the extension of market exclusivity will make companies even more suspicious toward the economic profitability of pediatric clinical trials.

Third, it is highly questionable whether the extension of market exclusivity is a rational and efficient investment of taxpayers’ money in the development of pediatric drugs. Just as unpredictable as the profits that a pediatric trial will yield for the sponsor are the costs to society for providing the incentive. As a result, the current incentives are out of control.

Redrawing the present incentives could enable to control budgets more rationally and efficiently and to set clear priorities in pediatric research. This would certainly advance the interests of minor patients in drug development while still encouraging that new drugs for the young are marketed.

Conclusion

In this article, seven ethical controversies in the current practice of pediatric clinical research have been explored: (1) the integration of research in therapy, (2) the education of clinicians, (3) the empowerment of families, (4) the harmonization of protocol review, (5) the assessment of non-clinical research objectives, (6) the control of placebo use, and (7) the provision of fair incentives for pediatric research conduct. For all of these issues, a clear view on the way forward is largely lacking, either because these issues have not been discussed in depth to date or because the existing debates have failed to generate a generally supported consensus. Nonetheless, these issues need to be addressed to facilitate the ethical conduct of pediatric research, the practical implementation of the ethical and legal frameworks governing pediatric clinical research, and the streamlined, transparent, and exhaustive protocol review. As a consequence, the establishment of a working consensus in these issues and the operational implementation of this consensus are of major importance for the ethical quality of pediatric clinical research conduct.

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Chapter 6: Access to investigational medicinal products for minors

Pinxten, W., Nys, H., Dierickx, K. (2010). Access to investigational medicinal products for minors. Ethical and regulatory issues in negotiating children's access to investigational medicines. Journal of Medical Ethics 36: 791-794.

Abstract

Patients who search for a better treatment, an increased quality of life, or even a chance to preserve life itself may claim to have an interest in accessing investigational medicinal products (IMP), particularly when no validated treatment for their disease or condition exists. For many, awaiting the uncertain and time-consuming process of converting an IMP into an approved drug may not appear a realistic option, as prognoses may be grim and a dramatic outcome may seem hard to avert. Gaining access to an IMP, however, often proves to be a difficult enterprise with a highly uncertain outcome. In addition, the process of seeking access to IMP is surrounded by various ethical issues that will be explored in this article. This paper explores the ethical concerns in two potential tracks of seeking access to IMP for minors: on an individual basis, or collectively, as a patient organization. In this discourse, several unique ethical and regulatory concerns related to the direct negotiation of access to IMP for minor patients are identified, with a focus on product safety, the recruitment of research subjects, the unnoticed entry of market mechanisms in the recruitment of research subjects, and the sidelining of third parties in the recruitment process. The paper concludes with a concise reflection on the way forward. The quest for access to investigational drugs is particularly relevant to pediatric practice, in which a significant share of the drugs prescribed has never been tested in children or labeled for use in the pediatric population.

Introduction

Patients who search for a better treatment, an increased quality of life, or even a chance to preserve life itself may claim to have an interest in accessing investigational medicinal products (IMP), particularly when no validated treatment for their disease or condition exists.[1] For many, awaiting the uncertain and time-consuming process of converting an IMP into an approved drug may not appear a realistic option, as prognoses may be grim and a dramatic outcome may seem hard to avert. Therefore, patients have been actively seeking access to IMP ever since the AIDS crisis in the 1980s.[2] Gaining access to an IMP, however, often proves to be a difficult enterprise with a highly uncertain outcome.

In general, there are two ways to obtain access to an IMP, of which participation in a clinical trial is the most obvious. Unfortunately, many patients will be denied access to clinical trials as they fail to comply with the eligibility criteria or because the sample of

research subjects is limited in number, time, or location. Alternatively, terminally ill patients can be granted access to IMP exceptionally under different types of compassionate use programs, several of which exist in the USA, the EU and Canada. For patients failing to access IMP through participation in a clinical trial or under a compassionate use program, there appears to be no systematic opportunity, not to mention a generally recognized right to access IMP, as is for example suggested in the paradigmatic case Abigail Alliance v von Eschenbach.[3 4]

The quest for access to investigational drugs is particularly relevant to pediatric practice, in which a significant share of the drugs prescribed has never been tested in children or labeled for use in the pediatric population.[5-7] As a result, the line between using IMP and prescribing medicines off- label may at times be very thin, and therefore in pediatrics, IMP may be appear appealing as any non-validated treatment prescribed off-label. However, as off-label prescriptions are part of therapeutic practice and using IMP is part of drug development processes, there is a profound difference between prescribing treatments off-label and opening up the access to IMP. As a result, strategies to open up access to IMP for children create unique and profound ethical and legal issues. As creating access to IMP is clearly perceived as an interest of some pediatric patients, these issues need to be addressed urgently.

In this paper, we explore the ethical concerns in two potential tracks of seeking access to IMP for minors: on individual basis, or collectively, as a patient organization. In our discourse, we identify several unique ethical and regulatory concerns related to the direct negotiation of access to IMP for minor patients, with a focus on product safety, the recruitment of research subjects, the unnoticed entry of market mechanisms in the recruitment of research subjects and the sidelining of third parties in the recruitment process.

Individual patients seeking access to IMP: an illustratory case

Sandra Massart, a Belgian girl aged 7 years with from metachromatic leukodystrophy, is rapidly declining in the absence of a validated treatment for her disease. Her parents devoted themselves indefatigably to provide her with Metazym, an IMP developed by the Danish firm Zymenex. Sandra could not obtain Metazym through participation in a clinical trial because –exceeding the upper age limit of 60 months- she did not comply with the eligibility criteria of the running trial. Therefore, the parents searched for an alternative way to obtain Metazym and claim to have negotiated that Zymenex would provide Sandra with Metazym under the named patient program on payment of approximately €45 000 per month, or €1 000 000 for 2 years of administration. Because the Belgian public health insurance rejected the parents' request to refund Metazym, an extensive media campaign was set up to raise the necessary funds. This campaign peaked when Belgium's largest commercial channel reported on Sandra's cruel fate during Christmas day's prime time newscast. In the following days, public indignation was nurtured and in no time the necessary funds were raised.

However, in sheer contrast to the rapid and easy fundraising, the family did not succeed in gaining access to Metazym. Shire, the British firm that had acquired Metazym by the time funds were raised, stated that they were unable to provide the family with Metazym, due to supply constraints.[8] Even when production restrictions are not applicable, litigation fears and public relations concerns may constitute a hurdle to the provision of an IMP at the request of an individual patient.[1 2]

Recently, Shire announced that they were stopping the trials of Metazym because of the low efficacy.

Obviously, this complex case raises many more ethical issues than that of access to IMP alone. However, in this paper, we will limit the scope of the ethical assessment of this case to the issue of access to IMP.

Negotiating access collectively: the collective claim of patient populations

The case of Sandra Massart clearly illustrates the interest in accessing IMP that may be attributed to individual patients. Similar to this individual interest in accessing IMP of individual patients, a collective interest in accessing IMP can be claimed by patients with the same disease. As a consequence, it is worthwhile to extend the scope of ethical reflection on the direct negotiation of access to IMP from the individual level to a group level. As patient organizations serve the collective interests of patients at such a group level, it is worthwhile to explore their potential role in negotiating the access to IMP collectively.

Theoretically, patient organizations are well placed to discuss and negotiate the access to IMP for the collective of their members. Not only do they increasingly present themselves as partners of the pharmaceutical industry in drug development,[9] their role in the field of clinical research also well exceeds that of individual research subjects,[10] providing them with a wide repertory of assets that may appeal to the producers of IMP. First, patient organizations are a major source of information to their members, and may raise enthusiasm as well as suspicion about clinical trials among them. Second, patient organizations may actively contribute to the success of clinical trials by facilitating the recruitment of research subjects, which is often difficult for pediatric clinical trials. In addition, patient organizations are well placed to create patient registries, which are of great importance to clinical research. Third, patient organizations may be willing to provide financial support to clinical research, which enables them to press on the research agenda and direct clinical research towards the experienced needs of the patients they represent. In addition, to a certain extent, acting as a research funder grants patient organizations a say in the design of clinical trials, including the eligibility criteria for trial participation. Holding these assets, patient organizations enjoy a privileged position in the negotiation of access to IMP, particularly with regard to IMP provided to research subjects in clinical trials.

Ethical and regulatory concerns

The negotiation of access to IMP, either by individuals or patient organizations, generates various ethical and regulatory issues that need to be addressed. In particular product safety, the recruitment of a sufficient number of research subjects, the unnoticed entry of market mechanisms in the recruitment of research subjects, and the sidelining of third parties involved in the recruitment process deserve specific attention in this respect.

Product safety

Obviously, the therapeutic nature of an IMP is contingent until its safety and efficacy have been tested, appropriate dosages and administration forms have been determined, and adverse effects have been identified. Therefore, the control of product safety of medicinal products is a time-consuming process,[11] and hastening access to these products will expose patients to considerable risks, as serious toxicities are often only detected in late stage drug development.[12 13] Nonetheless, the benefits of using IMP may appear plentiful to patients, and the odds are that for many patients the risks and therapeutic contingency of IMP will easily be overruled by their presumed benefits, particularly when no validated drugs exist, and time is pressing because patients deteriorate rapidly.[11]

However, in pediatric clinical research, product safety is of special importance as minors, in contrast to their adult counterparts, are most often considered incapable of taking full responsibility for voluntary risk taking. This renders it unethical to expose minors to research risks unnecessarily, not only in the sense that minors should not be exposed to unnecessary research risks, but also in the sense that no more minors than necessary should be exposed to research risks, regardless of their severity or acceptability. In this regard, based on the ethical principle of non- maleficence,[14] many ethical codes and legal regulations require that clinical trials of IMP are only conducted in as few minor subjects as necessary to obtain relevant research results. Therefore, opening up the access to IMP to more patients than required to gather relevant data raises serious ethical concerns, also when access is facilitated outside the setting of clinical trials.

The requirement to limit the number of subjects in clinical trials to a minimum, however, does not automatically rule out the compassionate use of IMP when patients enter a case beyond aid and no more therapeutic options are available. However, here, vulnerable parents who may be willing to spend fortunes on ill-founded hopes and despair should be protected against the drawbacks of an unregulated market. As medicinal products are subjected to strict licensing and marketing requirements for very sound reasons, any commercial supply of products -most often at an excessively high cost- appears ethically questionable. Therefore, we suggest that the provision of IMP for compassionate use should never be organized as a free market or by direct negotiation between the beneficiary and the producer. Quite the reverse, society should take the important responsibility of protecting all who have outreached the scope of therapeutic options against the devastating consequences that ill-founded hopes and despair may have. As IMP are to be situated at the frontline of medical innovation, one must question whether it is acceptable to send minors

to the front, acknowledging that the majority of IMP will not make it to validated drugs,[11] and the use of IMP is likely to expose more minors than necessary to considerable research risks.

The recruitment of a sufficient number of minor research subjects

The conduct of clinical studies in a sufficient number of eligible research subjects is indispensible to develop safe and efficacious drugs.[2 13] However, opportunities to access IMP outside of clinical trials are likely to interfere gravely with the already difficult recruitment of minor research subjects.[1 15] In particular, the many patients who seek to avoid random assignment will seek access to IMP outside of clinical trials, and may even try to render themselves ineligible for trial participation.[1]

Apart from these recruitment difficulties, permitting companies to provide unapproved IMP against payment contrasts sharply with the extensive efforts to encourage the pharmaceutical industry to invest in complex and expensive clinical trials,[2] including the provision of considerable incentives to compensate the poor profitability of pediatric drug development.[16 17]

Preserving recruitment from market mechanisms

Ever since the involvement of human subjects in clinical research has become the subject of extensive ethical guidance and legal regulation, considerable efforts have been made to preclude market rationales from becoming involved in the recruitment of minor research subjects. For example, in Europe, the provision of payments or other incentives to researchers, minors, and/or their parents has been regarded with great suspicion because of the bias and conflicts of interests such incentives may generate. However, when patients negotiate their access to IMP outside of clinical trial participation, market rationales tend to enter unnoticed.

For example, obtaining IMP outside of clinical trials comes at a price, which can be excessively high.[1] Also when patient organizations negotiate their members' access to IMP within clinical trials, market rationales tend to become involved. The fact that the owners of IMP have something of great interest to the members of the patient organization and that patient organizations own several assets of interest to the producers of IMP provides all the ingredients for market-driven exchanges. The unnoticed entrance of market mechanisms in pediatric clinical research cannot be reconciled with the ethical premises and legal requirements that have been governing pediatric research for decades now. Therefore, care should be taken that market rationales do not erode the voluntariness and altruism that traditionally underpin research participation.

Keeping third parties involved

Third parties, such as competent authorities, regulatory bodies, ethics committees and physicians who operate independently from the sponsor play an essential role in the design and conduct of clinical trials. However, the direct negotiation of access to IMP between patients and companies willing to provide IMP to them tends to bypass the timely

involvement of such third parties, releasing this form of experimental drug use from substantive scientific and ethical assessment.

While it is obvious that competent authorities, regulatory bodies and ethics committees will always have entry points in the development and supply of IMP, the involvement of physicians operating independently of the sponsor (e.g., hospital physicians agreeing to cooperate with a clinical trial and to recruit among their patients) tends to fade away when access to IMP is negotiated directly between patients and sponsors. Nonetheless, such physicians have several important opportunities to implement ethical standards in practice.

First, being committed to the treatment of their patients, physicians are well placed to assess whether an IMP, administered either within or outside a clinical trial, suits an individual patient against the background of the medical history, the current condition and the prognosis of the patient concerned. In consequence, physicians are well placed to inform their patients about all relevant aspects of using an IMP, which is likely to counter misplaced enthusiasm about IMP, similar to therapeutic misconceptions in clinical research.[18] Second, the relationship of trust that physicians have established with their patients over time appears to be an excellent situation in which to discuss the use of an IMP. Third, operating independently from the sponsor, physicians can easily refuse to recruit subjects among their patients when they judge that a study protocol is ethically unacceptable or does not serve the interests of their patients, even when the protocol has been approved by an ethics committee and the competent authority.[19] In this way physicians personally provide an additional ethical assessment of study protocols.

Conclusion and discussion

It is encouraging that new innovations in clinical research are considered to be of interest to minor patients, that hope in future scientific developments is cherished, that enthusiasm about new IMP is raised, and that minor subjects find themselves prepared to participate in clinical trials. Enthusiasm and hope, however, should not push the desire for health innovation beyond the ethical and regulatory safeguards that have been integrated into the procedures of clinical trials and alternatively in systems of compassionate use. However, in a setting in which a relatively large share of the drugs used have not been tested for safety and efficacy, such as pediatric health care, patients who seek a better treatment, an increased quality of life, or even a chance to preserve life itself may claim to have an interest in accessing IMP, and actively seek access to IMP, either individually, or collectively as a patient organization. In this article, four serious ethical concerns in the quest for access to IMP have been explored: (1) product safety; (2) the recruitment of research subjects; (3) the unnoticed entry of market mechanisms into the recruitment of research subjects; and (4) the sidelining of third parties in the recruitment process. These ethical concerns indicate that broadening the access to IMP is a very precarious enterprise that appears hard to align with existing ethical and regulatory frameworks. In addition, it is strongly to be discouraged that vulnerable parents are tempted to spend large amounts of money on ill-founded hopes and despair.

On the other hand, access to IMP can be provided legitimately, as is currently done within clinical trials and compassionate use programs. However, these ways of providing IMP have a number of constraints that are open to discussion. First, both clinical trials and compassionate use programs have no truly systematic way of determining which patients can be provided with IMP. This may appear manifestly unjust to the parents of children whose lives are at stake, and is therefore very likely to be hard to accept. Against this background, families may actively seek access to IMP, even outside of clinical trials and compassionate use programs, and backed by massive support from the media and the public at large, as the case of Sandra Massart indicated. Second, any determination of who is eligible for clinical trial participation is a result of scientific or policy choices, which are open to discussion and change. Therefore, notwithstanding the profound ethical concerns described in this article, patients, individually or collectively, may feel they have strong reasons actively to seek access to IMP.

Responding to the phenomenon of the direct negotiation of access to IMP adequately, however, is a complex challenge. A mere prohibition of access to IMP outside clinical trials and compassionate use programs is not sufficient in this respect, because the direct negotiation of access to IMP between patients and drug developers may also affect access within clinical trials or compassionate use programs. Three additional concerns are in need of ethical attention.

First, firm and realistic understanding about what is to be expected from healthcare and drug development should be nurtured in all actors involved. No matter how tragic the situation or how strong and emotional appeal to a last resort, it should always be recognized that IMP are no panacea. Opening up access to IMP will not discharge patients in need from irreversible, and at times cruel and fatal disease. Also, the fact that time may work against cure will not be resolved by opening up access to IMP (unless maybe in an extremely exceptional case). The recognition that disease can come as an inevitable tragedy is not to result in skepticism towards drug development but merely serves to show that the disadvantages of rushing a process as complex, contingent and risky as drug development are likely to outweigh the benefits. Against this background, one should be vigilant about what claims to health care we support as clinicians, patient organizations and society at large (including popular media, as the case of the family Massart clearly illustrates).

Second, ethical and regulatory guidance should enter the drug development process as early as possible, preventing direct partnerships between patients or patient organizations and drug developers from taking place in an underregulated environment. In contrast to the provision of IMP in clinical trials or compassionate use programs, partnership between patient organizations and drug developers as such is not specifically regulated or guided. This does not imply that such partnerships are to be avoided, but raises concerns about how ethical and regulatory issues are to be addressed, for example when such partnerships result in agreements that shape the research agenda or the design of future clinical trials. In particular, concerns related to the unnoticed entry of market mechanisms should be detected and addressed as soon as possible. Therefore, a timely involvement of third parties

in the partnership between patient organizations and drug developers, including experts in treatment, ethics and law is strongly recommended.

Third, it is both prudent and responsible to rely on important efforts to supply safe and efficacious drugs for the young that are currently being made. In the European Union and elsewhere, important efforts have been made to encourage and reward the development of safe and efficacious drugs for minors. Against this background, one must be particularly vigilant that recruitment for clinical trials is not hampered by efforts to facilitate or extend access to IMP. Although time consuming, the quest for better treatments and increased quality of life should obviously focus no regular processes of drug development in controlled clinical trials.

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Chapter 7: The pursuit of non-clinical research objectives in clinical research

Pinxten, W., Nys, H., Dierickx, K. (2009). Ethical and regulatory issues in pediatric research supporting the non-clinical application of fMR imaging. American Journal of Bioethics, 9(1), 21-23.

Abstract

Over the past decades, important efforts have been made to regulate the involvement of children in clinical trials. However, current ethical and legal procedures surrounding clinical trials in minors (US/EU) are not designed to consider and assess the non-clinical use of medical technologies such as fMRI, while non-clinical applications of pediatric fMRI cannot be developed without conducting clinical trials in children. In our comment, we discuss the diverse ethical issues related to the non-clinical applications of fMRI from the perspective of pediatric clinical trial regulation

Ethical and Regulatory Issues in Pediatric Research Supporting the Non-Clinical Application of fMR Imaging

Clinical research using fMRI enables to correlate brain activity to highly intimate human capacities and functions such as memory, character, or (anti-) social behavior. The results of such research offer a large potential for non-clinical applications, as Fenton and colleagues[1] point out in the target article. Pediatric fMRI is surrounded by myriad ethical issues[2] that are intensified in developing non-clinical applications of the technology, as such applications may introduce new paradigms in important social institutions, including education and jurisprudence. In this context, Illes and colleagues[3] rightly indicate that, even though such non-clinical applications are not validated, reliable or standardized to date, the time is right for a proactive ethical approach.

In addition to discussing the ethical issues related to the non-clinical application of pediatric fMRI, a proactive ethical approach should also reflect on the development of these non-clinical applications. As non-clinical applications of pediatric fMRI do not just emerge outside the clinical setting and their development requires the conduct of research in children, the ethical issues related to involving children in research are also highly relevant in this discussion.

In the US[4] and the EU[5], the conduct of pediatric research is guided by extensive ethical and legal frameworks that have been developed over the past decades. These frameworks consist of a large variety of ethical guidelines and national and international laws and share various ethical concerns that underpin them. In this commentary, we will explore how the ethical and regulatory frameworks that guide pediatric research are challenged by the

development of non-clinical applications of pediatric fMRI. In doing so, we will not provide an exhaustive overview or analysis of applicable regulation, but reflect on ethical values addressed in ethical guidance and legal regulation.

Ethical Issues Related to the Scientific Design of Pediatric Research

Two issues related to the scientific design of pediatric research raise serious ethical concerns: research objectives and research sponsorship.

First, clearly formulated and scientifically sound objectives are essential for research to be ethically acceptable. While at first sight it may seem obvious that research serves the advancement of biomedicine by generating progress in scientific knowledge or therapeutic options, this may not be the case in pediatric studies supporting the development of non-clinical applications of pediatric fMRI. We explicitly acknowledge that research supporting non-clinical applications of medical technology may not be clearly and easily distinguishable from research serving biomedical objectives. However, in our opinion, the direct biomedical relevance of certain studies, such as research gaining insight in religious experiences or moral deliberation, is open to discussion.

The large variety of research objectives—including therapeutic, non-therapeutic, and non-clinical objectives—that are pursued within the clinical setting may obscure the clinical relevance of research and the interests underlying research. In this respect, distinguishing clinical from non-clinical applications of pediatric fMRI may be helpful in searching for a moral justification of involving minors in research.

Second, and closely related to the issue of setting clear research objectives, is the issue of research sponsorship. Conducting research that serves non-clinical applications of medical technologies is likely to broaden the scope of interest in pediatric research from the scientific community and pharmaceutical industry to a large variety of commercial stakeholders searching for commercial applications of pediatric fMRI, such as reliable techniques for lie detection or methods to increase brand attachment. However, attracting investors who lack biomedical interest in research to fund pediatric studies will generate various ethical challenges, including dealing with conflicts of interests and creating appropriate professional standards.

Issues in Involving Minor Subjects in Research

Three major issues in involving minor subjects in research are intensified in the conduct of pediatric studies supporting non-clinical applications of fMRI: research risks, the impact of research on the well-being of minor research subjects, and informed consent and assent.

First, pediatric research supporting the realization of non-clinical objectives entails research risks, including physical and psychological risks[6] and social risks, such as medicalization, stigmatization, or neurodeterminism.[7]

As a general rule, risk-taking in pediatric research is strongly restricted by law. Most regulations require that research risks are either very low or justified convincingly by a benefit that counterbalances the risks. First, risks may be acceptable because the potential

to harm is very low. In U.S. federal regulation (45 CFR 46 subpart D, §46.404)[8] and the European Convention on Human Rights and Biomedicine (Art. 17),[9] minimal risk is explicitly defined as a risk threshold. Second, also risks exceeding this minimal level can be justified. The most common justification is proportionality between research risks and expected benefits. According to this rule of proportionality, the level of acceptable risks will increase as research generates more significant benefits. Benefits are valued higher in function of the therapeutic nature of research (therapeutic research is often distinguished from non-therapeutic research), and in function of the direct character of the benefit (a direct benefit to the research participant is generally preferred over benefits to more remote beneficiaries, such as the group of patients to which a minor belongs, the population of minors, or future patients or minors).

The risks assessed during the ethics review of research protocols, are strongly focused on the risks imposed on individual research subjects during research participation. The social implications of medical technologies—although very relevant in the case of pediatric research supporting non-clinical applications of pediatric fMRI—are not explicitly taken into account. Being non-invasive and overall low risk research (if fMRI devices are used correctly), pediatric fMRI tends to fall outside the scope of most risk parameters assessed by ethics committees.

Second, and closely related to the social risks of non-clinical applications of pediatric fMRI, is the ethical concern for the well-being of children. Pediatric fMRI—although non-invasive in clinical terms—has the potential of deeply entering the most private areas of the self, and therefore may have a serious impact on the lives of individual minors and of minors as a group. Most minors are unable to serve their own interests or to provide legally valid informed consent and are therefore protected against deception, abuse, or exploitation when participating in research. While the current protection of minor research subjects is focused on harms that are directly related to participation in research, the potential threats of non-clinical applications of pediatric fMRI well exceed the current scope of protection. In our opinion, serious efforts should be made to serve children's rights in the conduct of pediatric research supporting the development of non-clinical applications of pediatric fMRI. The collection of children's rights captured in the UN Convention on the Rights of the Child provides several interesting principles that can be used as a solid starting point in this respect.

Third, the conduct of research that supports the development of non-clinical applications of fMRI affects the process of obtaining informed consent and assent for participation in pediatric research. In particular the issue of providing clear disclosure of research sponsors and research objectives is intensified when research serves non-clinical applications. Nonetheless, clarity about conflicts of interests is essential for obtaining valid consent. In addition, important tacit processes in consent discussions, such as placing trust in the research and in researchers, may be compromised in absence of a clear disclosure of research objectives and sponsors.[10]

Conclusion

Non-clinical applications of pediatric fMRI entail both opportunities and threats in relation to the conduct of pediatric research and the interests of children. In a proactive ethical approach, the fact that non-clinical applications of pediatric fMRI challenge the current ethical and regulatory framework should not result inevitably in skepticism towards the development of such applications. Nonetheless, the conduct of pediatric research should be approached with caution, and various essential questions need to be addressed, preferably within the current legal frameworks regulating pediatric research.

First, it must be discussed how non-clinical objectives in pediatric research can be taken into account and ethically assessed. Current review procedures are ill-suited to take into account and assess non-clinical applications of pediatric fMRI, and it is open to discussion whether the biomedical scientific community should act as a gatekeeper guarding potential threats in the non-clinical application of medical technology. Nonetheless, explicit attention for non-clinical applications of pediatric fMRI in protocol review would certainly raise ethical sensitivity towards the individual and social threats that such non-clinical applications may entail.

Second, it must be cleared out whether the involvement of minors in research serving the development of non-clinical applications is acceptable and in which cases. Pediatric research is a precarious enterprise, and important efforts have been made to restrict the involvement of minors in research wherever possible. Pediatric research supporting the development of non-clinical applications of fMRI tends to bypass these restrictions, and therefore should be the subject of new regulatory efforts that can be established within the existing ethical and legal frameworks.

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Chapter 8: Distributive justice: funding the development and supply of orphan drugs

Pinxten, W./Denier Y.[i], Dooms M., Dierickx, K. (2010). A fair share for the orphans. Justice, rationality and arbitrariness in the allocation of limited healthcare resources to the prevention and treatment of rare diseases. [unpublished manuscript]

Abstract

For a significant number of patients, no or only poor interest in developing a treatment for their disease or condition exists. Especially with regard to rare diseases, the lack of commercial interest in drug development is a burning issue.

Several regulatory interventions have been made in to address the commercial disinterest in rare diseases. However, existing regulations mainly focus on the provision of incentives to the sponsors of clinical trials of orphan drugs, and leave the overarching question on the righteous place of orphan drugs in resource allocation systems unanswered.

In this article, we analyze major ethical issues in the development and supply of drugs for rare conditions. Subsequently, we propose an ethical framework, which can help health policy makers in moving forward in the difficult issue of justly allocating resources to the prevention and treatment of rare diseases.

Introduction

Orphan drugs are developed for the diagnosis, prevention, or treatment of life-threatening or chronically debilitating rare diseases, a significant share of which affects neonates and children. As for known causes, these diseases vary from genetic diseases, very rare infectious diseases, to auto-immune diseases and very rare poisonings.[1 2] It is estimated that 20 to 35 percent of all recognized diseases are rare diseases, the prevalence of which is below or equal to five in 10 thousand persons or less.[3 4]

Although the prevalence of individual rare diseases is by definition very low, rare diseases are a widespread phenomenon. At present, the worldwide number of rare diseases is estimated between 5 and 8000, affecting about 250.000 patients in the European Union. Notwithstanding the frequent occurrence of rare diseases among the European population, a significant share of these diseases has been relegated to therapeutic orphanage.

[i] The first and second author equally contributed to this manuscript

Several issues render the development and provision of drugs for the diagnosis, prevention, or treatment of rare diseases a precarious enterprise. For example, the scarcity and geographical dispersal of eligible research subjects make clinical research in rare diseases complex and expensive. In addition, the combination of the high cost of clinical trials and the small market for newly developed treatments often results in an uncertain return on investment under the regular market conditions.

Because the usual conditions for marketing drugs are likely to work against the development and manufacturing of drugs for the diagnosis, prevention, or treatment of rare diseases, this predicament needs specific attention in ethics and policy. In this respect, important efforts to provide adequate political support and scientific research programs in the field of rare diseases have been made worldwide[ii] over the past two decades. For example, in the EU, a specific regulatory framework has been created to encourage the development of "orphan drugs" (including the provision of financial incentives) for the diagnosis, prevention, or treatment of rare diseases. At the supranational level, this regulatory framework consists of two regulations (Regulation (EC) No 141/2000 and Regulation (EC) No 847/2000), that are directly applicable to all EU Member States. In addition, specific domestic laws of individual EU member states may also be applicable.

Article 3.1 of regulation 141/2000 stipulates that orphan designation is granted if the sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

The success of the regulatory interventions in the EU has been widely recognized,[2 5 6] and in the past decade, the European Medicines Agency has received over 1100 applications for orphan designation. Since the entry into force of the European Orphan Regulation in 2000, more than 700 orphan designations were granted, and more than 60 orphan designated medicines have been approved, offering new treatment options for over 50 rare diseases.[iii]

[ii] Specific programs exist for example in the US, Japan, Australia, Taiwan, and the EU

[iii] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/05/WC500090820.pdf

However, this success in encouraging the development of drugs for rare diseases did not discharge rare diseases from all the forces that drive them into orphanage. Apart from the well-known scientific and economical difficulties, a fundamental challenge resides in facing the opportunity cost of funding orphan drug development. Like Gericke et al.[7] have put it, the discussion of how much a society should spend on research and development of rare diseases represents a fundamental *moral dilemma*. On the one hand, each rare disease represents only a small number of individual patients within a particular society. Hence, investing substantial amounts of resources in rare conditions could be considered unethical from a utilitarian point of view, since this would not maximize the benefits of society. The opportunity cost, understood in terms of benefits foregone for others, of such a policy would be very high. On the other hand, it is reasonable to question the abandonment of individual patients who are affected by a serious but rare condition for which no treatment exists. Is it fair to simply deny support for research and development on the basis of a condition being rare? Many would disagree and uphold that (1) society has a moral obligation not to abandon the patients suffering from a rare disease, and that (2) medicine has a professional obligation to advance scientific knowledge in pursuing new therapies. In this paper, we analyze this dilemma by focusing on the following question: How can sufficient attention be paid to orphan drug research and development in a fair and equitable way (that is, in a way that it does not drain away all the resources from other important health care goals)? Starting from a normative reflection on the biomedical and ethical relevance of allocating limited resources to the development and supply of orphan drugs (Part 1), we design a framework, which serves as the ethical basis to provide a fair share of resources for the development and supply of orphan drugs (Part 2). The framework consists of a lexicographical structure of three principles, namely (1) fair budgetary insulation, (2) certain access for some, based on rational priorities, and (3) possible access for all, based on random selection. Figure 1 provides an overview of the various questions and tracks that we explore in this framework.

Part 1: Why we should care about the orphans

In all health care systems, there is a struggle to decide which health care services and technologies should be provided for patients within the system.[8] These struggles are particularly acute when considering pharmaceuticals. Which drugs are eligible for investment in research and development, as well as for reimbursement later on? In this discussion, criteria such as efficacy, need, prevalence, and cost-effectiveness are used in the assessment process, which makes orphan drugs not easily eligible for selection.[2] So, if we want to make out a case for the patients who suffer from a rare disease, we have to answer to the first and most basic normative question in this field: why should resources be allocated to the diagnosis, prevention, and treatment of rare diseases?

<table>
<tr><td rowspan="5">Normative Reflection</td><td colspan="3">Question 1: Should we fund the development and supply of orphan drugs?</td></tr>
<tr><td rowspan="2">1. Biomedical considerations</td><td colspan="2">CHECK 1:
Does the development and supply of orphan drugs
fit the objectives of health and healthcare?</td></tr>
<tr><td colspan="2">Yes!
The diagnosis, prevention, or treatment of rare diseases
is among the core objectives of medicine and healthcare</td></tr>
<tr><td rowspan="2">2. Ethical considerations</td><td colspan="2">CHECK 2:
Is the development and supply of orphan drugs
compliant with our concepts of justice?</td></tr>
<tr><td colspan="2">Yes!
The development and supply of orphan drugs is compatible with our concepts of justice</td></tr>
<tr><td colspan="3">Answer 1: Yes we should fund the development and supply of orphan drugs.</td></tr>
<tr><td colspan="4">From normative reflection to allocation policy:</td></tr>
<tr><td rowspan="5">Allocation Policy</td><td colspan="3">Question 2: How can we do this fairly?</td></tr>
<tr><td colspan="3">Hurdles: Practical modalities of allocating resources to orphan drugs
- prevalence
- efficiency
- efficacy
- opportunity cost
These hurdles create moral dilemmas with regard to fair allocation policies</td></tr>
<tr><td rowspan="3">3. Opportunity Cost</td><td colspan="2">CHECK 3:
Is the opportunity cost of orphan drugs ethically acceptable?</td></tr>
<tr><td>No!
In so far that the interests of the individual erode the common interests of social healthcare</td><td>Can this be avoided?</td></tr>
<tr><td></td><td>Yes!
<table><tr><td>If limits are set to the number of beneficiaries
Track 1:
Rational Priorities
Certainty for some
---conditional---</td><td>If limits are set to the chance of acquiring funds
Track 2:
Anne of Green Gables
Possibility for all
---unconditional---</td></tr></table>Moral qualities:
-acceptable opportunity cost
-non-abandonment</td></tr>
<tr><td colspan="3">Answer 2: Yes we can fund the development and supply of orphan drugs
While limited resources do not allow to abundantly provide resources to all, the opportunity cost of orphan drugs can be kept within rational boundaries, and the principle of non-abandonment can be fully implemented in resource allocation</td></tr>
</table>

Biomedical considerations

From a biomedical perspective, the development and supply of orphan drugs must be situated within the realm of the objectives of healthcare and medicine.

Contemporary health care is a complex and heterogeneous framework of institutions, services and policy measures that are generally organized in accordance with three goals: prevention, cure and care.[8] In general, public health measures contain the categories of services that promote the collective health status by means of prevention of disease and disability. Besides prevention, health care also includes the familiar personal medical services of cure and the social support services of care for the chronically ill or disabled. At first sight, these three pillars of health care are hierarchically structured: prevention is preferred to cure, and cure is preferred to care.

By preserving health, by restoring it when possible, and by caring for the patients when cure is not possible, offering them support and easing their suffering, health care institutions, services, and measures have a great impact on people's well-being. That is, they determine "the level and distribution of the risk of our getting sick, the likelihood of our being cured and the degree to which others will help us when we become impaired or dysfunctional".[9] Off course, a lot depends on the way in which health and disease – and *a fortiori* the principle aim of medicine - are being understood. Here, we can distinguish two representative theories.[10] The first is the narrow, biomedical model of health and disease according to which health is the absence of disease and disease is a deviation from normal, natural, species-typical functioning as human beings.[11-13] Health refers to normal functional capacity, whereas disease reduces this capacity to a level that is lower than the typical efficiency levels. The task of objectively characterizing normal functioning capacity falls to the biomedical sciences and is calculated statistically by comparison with an age group or sex within the human species. The second is the broad and more holistic model, in which cultural, historical and social factors are taken up in addition to factors of species-typical functioning. According to the holistic approach, health always has to do with the functioning of a person as a whole, as a social being, part of a network of relations. According to this theory, health is the ability of a person to attain vital goals under standard circumstances.[14]

In both theories, health is a broad concept that lacks inherent boundaries. This lack of boundaries is saliently illustrated by the World Health Organization's (WHO) definition of health. According to this definition, health can be defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Obviously, concepts as broad as the WHO definition of health have been fiercely criticized for their potential to outstrip the limited resources a society can devote to healthcare in an uncontrolled fashion. The tension between indefinite health aspirations and exhaustible resources prompts allocation policies to pursue justice and fairness in the distribution of available resources. In this respect, Daniel Callahan pointed out the absolute necessity to limit the aspirations that a society pursues in the public provision of healthcare, based on a

clear concept of the kind of life we want to live and what efforts a society can reasonably make to support the realization thereof.[15 16]

Obviously, setting limits to what we pursue in health does not leave the objectives of healthcare unreflected. While broad concepts of health may comprise myriad objectives (ranging from diagnosis, prevention and therapy to bodily aesthetics and human enhancement), safeguarding the fair and rational allocation of resources by setting limits to what health society supports for all does not seem compatible with such unbounded pursuit of health objectives. Therefore, it is important to situate the diagnosis, prevention, and treatment of rare diseases in relation to other health objectives.

The general objectives of prevention, cure and care are cornerstones of contemporary healthcare. Particularly with regard to life threatening or chronically debilitating conditions or diseases, diagnosis, prevention or treatment are to be considered as core businesses of healthcare, for their responsiveness to basic medical needs, as preserving life itself. This is by definition the case for the development of orphan drugs, and the low prevalence of rare diseases does not affect this compliance with the core objectives of healthcare in any way. By consequence, there appear to be no valid reasons to exclude rare diseases from the scope health objectives when limits are set to what is pursued in publicly funded healthcare.

Ethical considerations

Now that the diagnosis, prevention, and treatment of rare diseases have been situated at the core of biomedicines activities, the development and supply of orphan drugs must be aligned with our concepts of justice.

Theoretically, the share of available resources that is allocated to the diagnosis, prevention, and treatment of rare diseases can range from zero to unlimited expenses. However, both ends of this spectrum are clearly unethical. On the one hand, it is manifestly unethical to preclude rare diseases from public healthcare resources for its violation of the principle of non-abandonment.[7 17] Ignoring the healthcare needs of a population as large as that of all patients suffering from rare diseases simply cannot be ethically justified. In addition, orphan drugs can be regarded as essential medicines,[2 18 19] which are described by the WHO as:

> *The medicines that address the priority health care requirements of a given population. These medicines are selected through an evidence-based process with due regard to public health relevance, quality, safety, efficacy and comparative cost-effectiveness.*
>
> *A fundamental criterion for essential medicines is that they must be available within the context of functioning health systems, and always in suitable amounts and dosage forms. The selection of essential medicines is a cornerstone of national medicine policies and supports the smooth functioning of the entire pharmaceutical system.*[20]

On the other hand, unlimited expenses are out of the question, since the development and supply of orphan drugs –due to the limited nature of public healthcare resources, the high price of treatments and large number of diseases- clearly comes at the risk of outstripping the available healthcare budgets in an uncontrolled manner. While both unlimited funding and overall abandonment do not offer acceptable grounds for the allocation of resources, it is possible and necessary to adopt a middle course. On this track, the major challenge is to address the moral dilemma of opportunity cost. This entails that the resources that are devoted to the diagnosis, prevention, or treatment of rare diseases cannot be spent on the realization of other healthcare objectives. Thus, the allocation of resources to orphan drugs excludes other claims to the limited resources available. McCabe et al[21] illustrate this issue strikingly: "a drug costing £50.000 per patient per year, would only cost £2.5m a year of there were only 50 patients to be treated. However, the cost should not be considered without reference to the value of what is foregone. £2.5m would pay for over 520 hip replacements." Exactly this opportunity cost necessitates us to enquire whether the development and supply of orphan drugs can be reconciled with the different concepts of distributive justice that govern healthcare policies. In this respect, several traits of orphan drugs challenge the utilitarian and right-based approaches of justice that are commonly used in allocation policies.[7] First, several traits of rare diseases and orphan drugs work against efforts to maximize the benefit that is generated from limited resources. For example, research and development is hampered by a shortage of (reliable) data on various aspects of rare diseases,[2 5 19] difficulties in recruiting sufficiently large samples of research subjects.[22] In addition, serious concerns with regard to the cost efficiency of orphan drugs exist. Jointly, the low prevalence of rare diseases, the high costs of developing a drug, and the practical complexity of developing efficacious orphan drugs work against cost-efficiency. Nonetheless, cost-efficiency will play an important role in various accounts of distributive justice and in the way a health policy deals with opportunity costs. Because evidence base to assess cost-efficiency is lacking for many rare conditions, the allocation of resources to the development and supply of orphan drugs is practically complicated (but therefore not impossible) to reconcile with utilitarian concept of distributive justice. Here, the challenge in front of us is thus balance the undocumented and uncertain process of orphan drug development with the concerns efficiency and efficacy that play a prominent role in utilitarian accounts of justice. Second, the development and supply of orphan drugs cannot fully respond to the high claims rights based approaches make in the name of equity. While the mere low prevalence of a disease does not provide a valid ground to deny patients suffering from rare diseases from the benefits of medical progress,[23] non-abandonment does not automatically entail a full realization of equity in all of its different concepts (including equitable access, equitable resources, and equitable outcomes).[21] Even though patients who suffer from rare diseases are theoretically entitled to an equal claim to high quality healthcare as any other patient,[7 17] the limited nature of healthcare resources simply does not enable to provide every available or possible healthcare for all. Here, the challenge is to balance concerns of equity with the natural and artificial limits of the resources society devotes to rare diseases.

The fact that the allocation of resources to orphan drugs comes at an opportunity cost, obviously does not demonstrate the injustice thereof. Quite the reverse, any allocation of resources comes at an opportunity cost. In the specific case of rare diseases, several rationales may argue in favor of meeting the opportunity cost of developing and providing orphan drugs, provided that the resources expended on orphan drugs do not outshine other rational priorities in healthcare. Allocation policies thus face the challenging task to serve justice by providing a fair share of resources to the development and supply of orphan drugs without generating an unreasonably high (opportunity) cost. In support of this challenging task, we will now explore different strategies to allocate resources to the development and supply of orphan drugs in a responsible manner.

Part 2: Toward a Fair Share for the Orphans

Finding orphan drugs compatible with the core objectives of healthcare and with the concepts of justice that govern our allocation policies, does not offer a clear cut way to fund the development and supply of orphan drugs a controlled way. In response to the moral dilemmas in resources allocation to orphan drugs described in this paper, we therefore suggest three interventions to keep the allocation of resources to the development and supply of orphan drugs under control: (1) budgetary insulation, (2) certain access to resources for some (according to rational priorities), and (3) potential access to healthcare resources for all (at random).

Budgetary insulation

The designation of an orphan status to drugs for rare diseases has important consequences, as it turns the relatively weak claim to limited healthcare resources that individual rare disease have into a massive cumulative claim representing 5000 to 8000 diseases and over 250.000 patients in the EU. As a result, orphanage is turned from tragedy into opportunity, since the cumulative claim to resources of all rare diseases that obtain orphan designation is clearly too strong to be ignored in public policy. Opportunity, in turn, can even result in considerable success, as some drugs that were initially designated as orphan drugs in the U.S. eventually found a more common (e.g., AZT to block HIV replication) or also proved effective against more common disorders (e.g., EPO),[24] turning them in top-seller products.

The cumulative claim of rare diseases to limited healthcare resources also has important drawbacks that prompt public policy to balance rare diseases as a common phenomenon with rare diseases as rare conditions. Obviously, the strong cumulative claim of all rare diseases cannot just be extrapolated to every individual rare disease, as this would put unreasonable constraints to the allocation of limited public resources. Conversely, a budget comparable to that of a more common disease will not suffice to cover for the expenses of developing and supplying a drug for an individual rare disease. Therefore, the only rational response cumulative claim of all rare diseases is directed to the integer of rare diseases, rather than to individual rare diseases. This can be achieved by means of the budgetary

insulation of a share of resources to be dedicated to the development and supply of orphan drugs. In this way, an equitable share of resources can be provided to the integer of rare diseases in comparison with the integer of more common diseases, and equals can be treated equally. At the same time, diversity can be valued, as incentives can be provided to correct –to the extent possible- for of the dissimilarities between rare diseases and more common diseases. In addition, budgetary insulation will enable to generate progress in rare diseases, while firm limits can be set to prevent that the rare diseases outstrip the available healthcare budget.

While budgetary insulation can prevent the global healthcare budget from being disrupted by disproportionate cumulative claims and opens up real opportunities for allocating a fair share of resources to rare diseases, it does not solve the fundamental moral dilemmas in resource allocation. Inevitably, the insulated share of resources -regardless the available budget- is bound to be too limited to provide all for every individual. Therefore, the insulated budget rather relocates difficult choices on the allocation of resources to individual orphan drugs and rare diseases to a separate policy domain, than truly addressing the moral dilemmas underlying these choices. Therefore, budgetary insulation as such will prove an insufficient measure to handle profound ethical issues such as distributive justice, non-abandonment, and opportunity, and is only a prerequisite for an allocation mechanism, and not an allocation mechanism in itself.

Therefore, once a budget has been insulated, specific allocation mechanisms must find their entrance into health policy. We suggest two tracks of research allocation in this respect (1) certain access to resources for some (according to rational priorities), and (2) potential access to healthcare resources for all (at random).

Certainty for some: rational priorities among individual rare diseases

First, among comparable claims, rational priorities can be set. In this regard, Heemstra et al. have identified several predictors for the authorization of orphan drugs, related to (1) the company that develops the drug, (2) the pharmaceutical innovation performance, and (3) disease specific factors, including the prevalence, disease class, and disease-specific scientific output.[25] Also the well known NICE proposal for the appraisal of orphan drugs for very rare diseases is exemplary in this respect.[26] According to this proposal, three criteria can direct the allocation of limited resources: (1) the severity of the disease, (2) evidence of health gain, and (3) the life-threatening nature of the disease. Although it is open to discussion what criteria should be used to set rational priorities among the claims to resources within the bulk of orphan drugs, it is beyond doubt that (imperfect) criteria can and must be set, because clear priorities are indispensible to establish a rational, controlled, and efficacious use of limited resources. On the other hand, however, setting priorities in resource allocation also incorporates important drawbacks. In any set of priorities, certain diseases or conditions will fail to move up on the priority scale, rendering them practically untreatable. In addition, setting priorities also entails a considerable opportunity cost, as giving priority to one rare disease, will block the claim to recourses of another. To a large extent, rational

priorities are an efficient way to arrange the distribution of the limited resources that are allocated to rare diseases. Nonetheless, they do not suffice to constitute an overall fair distribution of resources. In any set of rational priorities, certain conditions will lack the assets required to move up on the priority list, and would therefore face eternal exile to orphanage, and by extension, non-explicit abandonment. Therefore, we suggest a second track of resource allocation to correct for this downside.

Possibility for all: the non abandonment of Anne of Green Gables-track

Since there are no valid reasons to principally preclude any patient suffering from a rare disease from having a rightful claim to the available resources (cf. principle of non-abandonment), also the rare diseases that fall outside the scope of rational priorities should be granted opportunities to acquire a share of the available resources. Keeping the access to limited resources open to all patients, however, cannot be done by means of rational priorities. Therefore, a complementary system of resource allocation, in which every orphan has a real -be it uncertain- chance to adoption, is necessary. In addition to allocation according to rational priorities, we therefore suggest a second track of resource allocation in which all patients suffering from rare diseases are granted a real (and not a merely theoretical) chance to obtain a share of limited resources for the diagnosis, prevention, and treatment of their disease. In this way, even the orphans that no one would rationally want to adopt –the Anne of Green Gables-like orphans[iv]- acquire a realistic, be it small, possibility of adoption.

To prevent this second track from outstripping the first track of resource allocation (i.e. allocation according to rational priorities), also here, budgetary insulation is indispensible. In addition, allocation in the second track should be organized 'at random', to move to the unrecalled territory beyond opportunity cost considerations and rational priorities (which generate new forms of abandonment). Such random allocation is analogous to the lowering a lifeboat at a random place among a group of drowning persons, while the boat is to small to carry all of them: nor does it preliminarily excludes anyone form being saved, neither does it decide in a rational way upon who should get priority. It is a rescue addressed to all, even though tragically, all can never be rescued with the resources at our disposal. By consequence, the random allocation of a minor share of resources is potentially more than just an inefficient and irrational system of resource allocation, since if used complementary to rational priority setting, it may turn rationality (which in itself is not necessarily compassionate) and compassion (which needs not to be rational) into a perfect match. In this sense, criticism on both setting rational priorities and random allocation can be addressed adequately.[27 28]

[iv] Cf. the novel of Lucy Maud Montgomery. Anne of Green Gables is the orphan that does not match the profile that the adoption parents had in mind.

Summarized, the second track of resource allocation (Anne of Green Gables) grants all patients suffering from an rare disease, even those who would never attract the attention in rational priority lists, a limited though real chance to be adopted in funding policies. This track is complementary to our first track (rational priorities), which ascertains that the efficient use of resources is to large extent pursues, as any rational and just healthcare policy would require. Combined, these two tracks respond adequately to the main moral dilemmas that underlie the allocation of resources to orphan drugs (cf. infra).

Conclusion

The provision of public healthcare depends upon limited resources to which many patients apply. No matter what efforts are made to dedicate public resources to healthcare, any share of resources a society can devote to health will prove to be insufficient to fully realize the open-ended objectives of healthcare. This has profound implications for rare diseases, many of them tend to have a rather weak claim to public resources, for reasons that include the limited availability of data about the disease, the opportunity cost, and the high price and the low cost-efficiency of drugs for the diagnosis, prevention, and treatment of rare diseases. Nonetheless, orphan designation has transformed the weak claim individual rare diseases could make to limited public resources into a strong, cumulative claim that cannot be ignored in European health policy.

In this paper, we have suggested a conceptual framework for the allocation of a fair share of limited healthcare resources to the diagnosis, prevention and treatment of rare diseases. This framework consists of three complementary parts. First, budgetary insulation of resources devoted to orphan drugs is a prerequisite, both to avoid that the strong cumulative claim of rare diseases to limited healthcare resources would outstrip the available budgets, and to enable that resources can be allocated in a controlled way. Second, the fair distribution of an insulated budget for the development and supply orphan drugs among the competing claims of individual patients and diseases, will clearly benefit form clear and rational criteria for priority setting. Notwithstanding the absolute need and clear advantages of setting rational priorities, however, priority setting does not suffice to provide all patients suffering from rare diseases with a real chance to attract funds for drug development and supply. Therefore, a second track of resource allocation, embedded in an insulated part of the budget allocated to orphan drugs, should grant all patients a real, though limited chance to see their claim to resources granted. This can only be achieved through a form of random allocation of a very small part of resources among the patients and diseases with the weakest claim to resources.

Allocating resources over two asymmetrical trails (rational priorities and random allocation) enables our public healthcare systems to afford “common rarity”. While it must be recognized that not all can be done for everyone –a premise the application scope of which is not limited to the rare diseases- something can possibly be done for all, and certainly for some.

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Part III

Integrating ethical and legal guidance in pediatric clinical research an empirical exploration

Chapter 9: Empirical exploration of the implementation of ethical and legal guidance in pediatric clinical research

Pinxten, W., Nys, H., Dierickx, K., Van Geet, C. (2010). The implementation of the European Good Clinical Practice Directive in informed consent discussions [Submitted for review].

Abstract

Objectives: In this chapter, practical issues in implementing ethical and legal requirements in pediatric research practice are empirically explored. The findings that are presented serve as a first illustration of how empirical enquiry can be integrated in the analysis of ethical, legal, and social aspects of pediatric clinical research, using the conceptual framework that has been developed in this doctoral thesis (cf. chapter 1). In addition, the findings that are presented in this chapter aim at informing the normative discussion of major tensions in pediatric research practice empirically (cf. general discussion). The analysis in this chapter focuses on the implementation of the national and supranational legal frameworks governing pediatric clinical research in informed consent discussions.

Methods: Practical issues in the operational implementation of ethical and legal requirements in pediatric research practice are empirically explored by means of an observational study of 23 informed consent discussions. Recognizing that the European legal framework imposes a single set of legal requirements to a large diversity of pediatric clinical trials, consent discussions were observed for a large variety of studies, diseases, sponsors, and study designs. The discussions were audio taped, transcribed, coded and analyzed qualitatively, linking the content of the informed consent discussions to three major concerns in the European legal framework. Only oral communication was taken account, even though additional written information was provided to the parents and/or minor subjects.

Against the background of the modest objectives of this empirical exploration, the limited sample size, the explicit choice to study pediatric clinical research in its full heterogeneity, and concerns to protect the anonymity of the clinicians, minors, and their parents involved, some types of analysis have been abandoned. In this respect, no links between observations and specific studies have been made, and no counts of the number of cases in which particular observations were present are given, since this type of analysis is likely to create a deceptive view.

It is fully acknowledged that the analysis does not generate any generalizable knowledge, and that the findings presented in this chapter could not be saturated within the limits of this empirical exploration. Nonetheless, the findings in this chapter suggest a number of issues that are highly relevant to analyze and discuss the operational implementation of ethical and legal requirements in pediatric research practice. As such, this analysis serves as

a first inventory of practical issues that can inform (1) pragmatic decision-making and (2) the design of further, more comprehensive clinical research.

Results: From the observed consent discussions, there are few indications that European legal good clinical practice (GCP) requirements are systematically implemented. We found no indications that the European legal framework offers strong impetuses for the realization of legal GCP-requirements at the interpersonal level of addressing ethical issues.

In addition, our analysis sheds a new light on five important ethical tensions: (1) harmonization versus heterogeneity (2) informed consent versus documented consent, (3) assent versus procedure compliance, (4) direct benefit versus valid research results, and (5) risk-benefit ratio versus risk-risk ratio.

Conclusion: It is both relevant and important to define and support the tasks, roles, and interests of minors, parents, and researchers in the informed consent process. Our observations draft a background against which these tasks, roles, and interests can be explored. Furthermore, our analysis sheds a new light on five important ethical tensions: (1) harmonization versus heterogeneity (2) informed consent versus documented consent, (3) assent versus procedure compliance, (4) direct benefit versus valid research results, and (5) risk-benefit ratio versus risk-risk ratio. In the general discussion, these tensions are discussed against the background of this observational study and other studies of informed consent for (pediatric) clinical research.

Introduction: Ethical and regulatory guidance of pediatric clinical research conduct

In the European Union (EU), pediatric clinical research is governed by a supranational legal framework that mainly consists of three landmark documents:[1] the Clinical Trial Directive[2], the Pediatric Regulation[3], and the Convention on Human Rights and Biomedicine[4] (and its additional protocol on biomedical research[5]). In addition, domestic legislation of individual member states may be applicable.[6 7]

The supranational legal framework regulates ethical issues at two levels. Issues with regard to the research design, the quality of research, and the practical modalities of research conduct are handled at the *institutional level*, where institutional bodies (such as the European Medicines Agency (EMA), competent authorities, and/or research ethics committees) are charged with the assessment of several aspects of research protocols. The urgency to deal with ethical requirements at the institutional level is very high, since this is a prerequisite to start any clinical trial. Once a protocol has been approved and recruitment starts, ethical issues move from the institutional level to the *interpersonal level* and present themselves on a case-by-case basis. At this level practitioners must deal with ethical issues in practice while interpreting and implementing generally formulated legal requirements. In contrast to the institutional level, compliance with regulatory requirements at the interpersonal level is hardly monitored or documented, except for the collection of written consent documents.

comparative overview of ethical and legal guidance at the institutional and interpersonal level

	Institutional level	**Interpersonal level**
Ethical Issues	research design the quality of research the practical modalities of research conduct	personal concerns and values of the actors involved
Assessor	institutional bodies, such as the EMA, competent authorities, and/or research ethics committees	(principal) investigator
Timing of assessment	prior to the start of the trial specific issues are monitored during the trial	from recruitment until termination of the trial
Response to ethical issues	meticulous well documented	subjective and unsystematic undocumented (except for the collection of signed consent forms)

In this paper, the main legal requirements at the interpersonal level, which are set down in article 4 of the Clinical Trial Directive, are used as a starting point for the analysis of observed consent discussions.

BOX 1:

Clinical Trial Directive (Directive 2001/20/EC)

Article 4 – Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Legal requirements at the interpersonal level

Article 4 of the Clinical Trial Directive regulates three main ethical concerns: (1) voluntary informed consent, (2) the provision of incentives, and (3) the benefits, risks and burdens of a pediatric clinical study.

Informed consent

As a legal doctrine, informed consent formally settles the agreement to enroll a research subject in a specific research protocol. In this respect, the Clinical Trial Directive requires that:

(1) the parents or another legal representative grant informed consent prior to the inclusion of a minor subject in a clinical study. This proxy consent is subjected to all legal standards for consent applicable to the consent of competent adults and must represent the presumed will of the minor concerned;

(2) minors are informed by a qualified person about the trial, the risks, and the benefits, at a level appropriate to their understanding;

(3) dissent -the explicit wish of a minor to refuse participation or to be withdrawn from the clinical trial- is considered by the (principal) investigator, in so far that a minor is capable of assessing information and forming an opinion.

The voluntariness of research participation is emphasized, since article 4(a) of the Clinical Trial Directive states that consent can be revoked at any time, without negative consequences for the minor.

Incentives

The Clinical Trial Directive does not allow any incentives or financial inducements except for compensation. Unfortunately, this clear prohibition of payment does not provide clarity in the sensitive area of compensation. While it is obvious that refunding a train ticket is unproblematic, the acceptability of offering a symbolic compensation for sacrificing several hours of (spare) time to a clinical study remains a source of controversy.[8-11]

Benefits, risks, and burdens

Requiring that “some direct benefit for the group of patients is obtained from the clinical trial”, article 4(e) introduces the enigmatic concept of a “direct group benefit”. While traditionally, a group benefit indicates that research is expected to generate a benefit other than a direct benefit to the individual subject concerned, the formulation in the directive mixes up direct benefit and group benefit. In a minimalistic interpretation, this provision would at least require that research results are of some interest to the population of minors or another group to which the minor subject belongs (such as the population of patients with the same disease, or the group of minors). The requirement that research must either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors, is consistent with such interpretation.

In addition, article 4 (g) stipulates that clinical trials be designed to minimize pain, discomfort, fear and any other foreseeable risk.

Scope and methodology

23 consent discussions concerning the enrollment minors in clinical trials were observed in a Belgian academic hospital. Because the European and Belgian legal frameworks impose the same sets of legal requirements to a large diversity of pediatric clinical trials, consent discussions were observed for a large variety of studies (n=12), diseases (acute and chronic, common and rare), sponsors (academic and industrial), and study designs (drug trials, diagnostic trials, placebo controlled and active controlled etc.). The duration of the discussions ranged from 3'43" to 74'46". In two consent discussions, an interpreter translated the conversation. The age of the minor subjects concerned ranged from 2 to 15 years.

All research subjects except for the healthy volunteers entered the research setting while seeking to deal with their disease or condition, either at their own initiative (in the follow-up of a chronic condition or prompted by an unexpected disease), or in response to a researcher's invitation to consider participation in a trial. The healthy volunteers in the study were recruited as a sibling or friend of diseased patients.

The discussions were audio-taped, transcribed ,coded and analyzed qualitatively, linking the content of the informed consent discussions to three major concerns in the European legal framework. Only oral communication was taken account, even though additional written information was provided to the parents and/or minor subjects.

Against the background of the modest objectives of this empirical exploration, the limited sample size, the explicit choice to study pediatric clinical research in its full heterogeneity, and concerns to protect the anonymity of the clinicians, minors, and their parents involved, some types of analysis have been abandoned. In this respect, no links between observations and specific studies have been made, and no counts of the number of cases in which particular observations were present have are given, since this type of analysis is likely to create a deceptive view.

It is fully acknowledged that the analysis does not generate any generalizable knowledge, and that the findings presented in this chapter could not be saturated in within the limits of this empirical exploration. Nonetheless, the findings presented suggest a number of issues that are highly relevant to analyze and discuss the operational implementation of ethical and legal requirements in pediatric research practice. As such, this analysis serves as a first inventory of practical issues that can inform (1) pragmatic decision-making and (2) the design of further, more comprehensive clinical research.

The protocol for this observational study was approved by the competent Ethics Committee, and oral informed consent was obtained form all the parents after providing them written information about the study. Assent was obtained from minors unless they

were incapable of providing it. All researchers who participated in the study provided written consent for their participation in the study.

Implementation of legal standards

Informed Consent

Motivated participation

While legally, willingness to participate in a trial is a matter of voluntariness, in practice, the motivated commitment of minors and their parents is essential for any clinical trial to succeed. During the observations, minors did not explicitate any motives to participate in a clinical study. Notwithstanding their overall willingness to discuss research participation and to grant informed consent, also the parents did not explicitate much of what drives them towards research participation. Still, three interrelated parental motives for participation in research were identified:

(1) pursuing an improved management of the disease, by increasing scientific knowledge and creating new therapeutic options

(2) addressing personal questions and uncertainties (for example, in one case the parents clearly regretted that some questions they had about the disease would remain unanswered in the study);

(3) creating a direct benefit for the child (as one parent explicitated: "I'm only interested in what's best for her [the patient]. Whatever you say is good for the child, we'll do it").

Apart from these parental motives, six motives for research participation were provided by the medical practitioners we observed, four of which are *functional motivations*:

(1) acquire access to medicinal products that are otherwise not available (during the trial, and sometimes also after the termination of the trial);

(2) increase the clinician's knowledge about various aspects of the disease;

(3) improve the management of the disease, maybe even generate a therapeutical breakthrough;

(4) help others, such as the next generation of patients suffering from the same disease.

In addition, two *factual motivations* indicated the low threshold to move from the current therapeutic scheme to research participation:

(5) opting for off-label treatment or a clinical study was largely a matter of the parent's preference since in practice, research participation would hardly be experienced different than off-label treatment;

(6) research participation is a common option since (nearly) all children (with the same condition) at the (i.c. pediatric oncology) ward were enrolled in a clinical trial.

Obviously, these motives were introduced on a case-by-case-basis and cannot just be extrapolated to informed consent discussions in general.

Information

In the observed consent discussions, information was not limited to information about the study concerned. Quite the reverse, in the majority of observed discussions the share of information about the trial was considerably small compared to the share of information about the disease, the condition of the individual minor, how the disease is to be managed, and miscellaneous practical and social issues.

Depending on the case, consent discussions served multiple purposes, a first set of which is related to research, addressing:

(1) a specific trial, for which informed consent was requested, or;

(2) research in general (for example when clinicians requested informed consent to take a blood sample for undefined research purposes), or;

(3) upcoming trials, to raise enthusiasm about upcoming research (for example, in one case, we observed four different upcoming protocols being explained to the minor and the parents), or;

(4) trials in which the minor cannot participate, because he or she does not comply with the eligibility criteria or because no more patients are being enrolled in the study (for example, one clinician explicitated: “If you here talking about this trial, you know why you’re not in…”).

Apart from research-related issues, a large variety of other health-related issues was discussed. For example, consent discussions that were held shortly after the diagnosis were employed to initiate minors and parents to the disease and how it is being managed. In addition, miscellaneous practical and social issues were discussed during the informed consent discussions, including educational issues, parenting, work-life balance, travel, the need for information and support for siblings, and even haircuts.

Often, information about the clinical trial was clearly embedded in the therapeutic context of the minor subject. In this respect, we observed:

(1) information about research participation being framed in the diagnosis and/or therapeutic context of the minor concerned;

(2) research protocols being used to explain regular therapy (for example, the standard of care was explained as the execution of the protocol without being registered in the trial, or as one particular arm of a randomized study; in one case, a study protocol was used to explain the standard of care, even though no more patients were included in the study);.

(3) parents‘ questions about the disease and its treatment being answered in reference to current or future research;

(4) parents enquiring whether their particular concerns (e.g., gaining insight in the etiology of the disease) were being investigated, as part of the protocol discussed or elsewhere.

Administration

The clinicians, parents, and where applicable minors that we observed expended considerable effort to comply meticulously with the administrative dimension of informed consent. Several issues needed to be cleared out, such as who had to sign where, what was the exact date, how many signed copies were needed, or what minors should do when they are asked to sign but had no signature.

In one study in which friends of patients were recruited as healthy volunteers, the recruitment strategy challenged the documentation of consent, since the healthy volunteers joined the patient and its parents to the hospital in absence of their –own parents.

Timing

The timing of the informed consent process clearly exceeded that of the observed discussions. Frequently ,reference was made to previous communication or to future opportunities to discuss research participation, and in general, parents were given ample time to consider the protocol before signing.

Also information was spread in time. In complex protocols, the information provided at the time of the observed discussion was most often limited to (1) a general outline of the trial and (2) detailed information on a first set of interventions in the near future. Here, clinicians explicitly indicated that they provided a lot of information in a very short time. Parents, in turn, did not request any further details.

Participation of the minor

In the observed consent discussions, the communication between minors and the researchers clearly focused on the disease and its management. When researcher explicitly addressed minors about the clinical trial, the interaction focused on the minors' understanding of what had been explained and his or her willingness to participate in the trial. Rare efforts to increase the minors' involvement in the consent discussion were unsuccessful, due to a clear lack of response from the minors' part. Overall, minors showed little interest in discussing research participation.

Apart from a few healthy volunteers who enquired how much time the investigation would take and whether it would entail the use of needles, no questions about the research were asked by the minors in this study. In addition, minors responded to questions about their participation in research a very concise and affirmative way, and showed no interest in discussing specific concerns in research participation.

Four types of observations indicated a low level of involvement in the discussion:

(1) the minor did not attend the informed consent discussion (all minors in this situation were younger than 6 years old and hospitalized);

(2) the minor was clearly too young to have an active role in the discussion;

(3) exhausted by the illness, therapy and/or emotions, the minor showed no interest in (full) participation in the discussion, even though maturity and age would not be an obstacle

(4) the minor did not demonstrate any interest in discussing participation in a trial.

When minors were asked to read an information leaflet, they always did so. Most of them took ample time to read the document.

Parental concerns

Most parents did not discuss specific research-related concerns. Nonetheless, based on the questions that parents asked during the observed consent discussions (the majority of which was formulated in only two cases), a considerable variety of parental concerns was identified, related to the:

(1) access to the study drug after the trial (also in the in the case that the minor would have been given a placebo):

(2) research design, more specifically:

(3) the way in which knowledge is created;

(4) specific research designs (e.g., randomization, wash out, placebo control);

(5) uncertainty about the best intervention (e.g., in the case of randomization);

(6) the role of the child (e.g., one parent checked: “it’s not that my child is going to be a guinea pig, right?”);

(7) benefits (e.g., advantages of the study drug compared to the current therapy);

(8) burdens (particularly practical issues, including the scheduling of follow-up visits or the frequency of collecting blood samples);

(9) risk to harm (including the risk of not being in the study);

(10) compatibility with other treatments (e.g., interaction between the study drug and other drugs a minor takes)

(11) adverse effects (e.g., how adverse effects can be recognized, whether potential adverse effects are reversible, and what intervention will be made in case adverse effects would occur).

Incentives

In one study, cinema gift vouchers were provided to the participating minors. This incentive was not discussed during the consent discussion, even though in two instances, the vouchers were handed during this discussion. The incentive has never been mentioned before consent was given, and has not been used during the discussion to persuade minors to consent (we have not studied the recruitment process, where the provision of this incentive may have played a role…).

In one case, the mother of a research subject provided an incentive for her son, as a reward for giving a blood sample.

Risks, burdens, and benefits

Benefit

In the observed consent discussions, hardly any explicit attention was paid to the (direct) benefits that the research was expected to generate. Most often, the topic was ignored altogether, and when benefit was discussed, its contingency was strongly emphasized. In one study, however, the potential benefits were related to the individual research subjects, linking the trial to a decrease of the "problems" that the patient experienced. Also the long time required to get a clear view on the true benefits was emphasized at several instances.

Notwithstanding this reticence to discus the potential benefits of a specific trial, the benefits of clinical research in general were discussed regularly. For example, clinicians suggested that research enables them to help children better, and can result in an amelioration of the current therapeutic standards. Similarly, reference was made to the positive impact of previous research on the current prognosis.

Risk to harm

Like it was frequently emphasized that the trial would not necessarily generate a benefit, it was equally emphasized that the harm, no matter how rare the incidence, might be inflicted to the subject concerned. At the same time, parents were often reassured that in the personal experience of the clinicians, no problems were experienced to date, even though many children had already used the drug. Where applicable, the risks of the trial were explained extensively, often in reference to the written information provided to research subjects. In the majority of observed studies, however, the risks of being in a trial were either very low (and comparable to the risks of the (off-label) standard of care) or similar to the risks of non-treatment.

Only in one case, it was explicitly stated that the study was designed to minimize harm. However, the topic of minimizing harm was frequently discussed when clinicians stated that the potential risks would be monitored carefully and that the adverse effects would be kept under control in case they would occur.

Minors did not interact in the presentation of risks. The concerns discussed by the parents related to the reversibility of harm, rather than the risk to harm as such.

Burdens

In the consent discussions we observed, the following burdens were discussed:

(1) additional visits to the hospital;

(2) having blood samples taken;

(3) fasting;

(4) missing school (or waking up early on a holiday to get to the hospital if you don't want to miss school);

(5) spending time in the waiting room;

(6) the frequency and duration of the procedures;

(7) the difficult compatibility with family life (for example the planned activities of all family members or the religious calendar).

At several instances, the minors in this study asked questions about burden-related issues, such as the number of interventions that would be done, the duration of the research or of a particular intervention, or the use of needles in a test. Most of all, however, observations revealed that minor experienced their task to deal with a disease, including the unpleasant aspects thereof, as a *fait accompli*. In addition, we did not observe any indication that minors make a distinction between research interventions and therapeutic interventions in this respect.

A significant part of the discourse on burdens focused on the practicalities of research participation, and clearly provoked more interaction of parents than any other topic. This is not surprising, given that parents have a key role in handling the practical burdens of research participation, including hospital visits, log keeping, and reporting potential adverse effects or adverse events.

Conclusion

The European legal framework sets down several requirements for Good Clinical Practice at the interpersonal level. In the oral communication during the consent discussions we observed, little demonstrated a true implementation or interpretation of these legal requirements. In addition, we found no indications that the European legal framework offers strong impetuses for the realization of legal GCP-requirements at the interpersonal level.

Therefore, it is both relevant and important to define and support the tasks, roles, and interests of minors, parents, and researchers in the informed consent process. Our observations draft a background against which these tasks, roles, and interests can be explored.

Furthermore, our analysis sheds a new light on five important ethical tensions: (1) harmonization versus heterogeneity (2) informed consent versus documented consent, (3) assent versus procedure compliance, (4) direct benefit versus valid research results, and

(5) risk-benefit ratio versus risk-risk ratio. In the general discussion, these tensions are discussed against the background of this observational study and other studies of informed consent for (pediatric) clinical research.

Acknowledgement

The authors are grateful to the parents, minors, and clinicians who participated in the study.

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General Discussion

Against the background of our analysis of ethical literature, health law, and empirical data we will now discuss seven ethical tensions: (1) standard of care versus state of the art disease management, (2) protection versus trust, (3) regulation versus discretion, (4) harmonization versus heterogeneity, (5) informed consent versus documented consent, (6) assent versus procedure compliance, and (7) direct benefit versus valid research results. The discussion of these seven tensions is illustratory for the contribution of this dissertation to the elucidation of ethical issues by means of contextual analysis, normative qualification, and practical guidance.

It needs to be emphasized that the formulation of ethical tensions in terms of conflicting concerns is by no means intended to suggest a polarization of ethical stances. Quite the reverse, as explicitated in the discussion of each tension, a well-considered middle ground is endorsed.

Standard of care versus state of the art disease management

In a human experience as striking and intimate as disease, uncertainty may come as a highly disturbing reality. Nonetheless, in pediatrics (much more explicit than in many other healthcare settings), uncertainty is everywhere. For example, the high rate off-label prescriptions[1-4] clearly illustrates that uncertainty about the effects of medicinal products is a common phenomenon. Consequently, a significant number of therapeutic interventions in pediatric practice essentially tend to be “an educated guess”, consisting of unsystematic and uncontrolled medical experimentation.

Although pediatric clinical trials are clearly the way forward in reducing the widespread uncertainty in pediatric practice,[5] the focus of ethical attention has traditionally been on the uncertainties in clinical research rather than on the reduction of uncertainties in therapeutic practice. For example, the expected direct benefit to the subject, the risk to harm, and the potential burdens have all acquired a central position in the assessment of the ethical nature of clinical research. Accordingly, therapeutic practice has been qualified as ‘standard’ (the *standard of care*), while clinical research has been qualified as ‘exception’.[6] Given the stringent lack of validated medicines in pediatric research, however, it is not clear to what extent such research exceptionalism serves the interests of minors who are in search of safe and efficacious therapy. For example, it is not clear whether patients are better served outside of clinical trials.[5 7] Quite the reverse, several important arguments make out the case for a better management of diseases within clinical trials: clinical trials (1) are conducted in a controlled setting, (2) entail a closer follow up of the patient, and (3) are conducted by clinicians who work at the state of the art of science and have primary access to newly generated evidence. An adequate management of a disease may therefore encompass clinical research and, from a scientific point of view and dependent on the specific case concerned, even give preference to participation in a clinical trial over the standard of care.

While clinical research must obviously remain subjected to extensive scientific and ethical assessment, aspiring a *state of the art disease management* in stead of the provision of an established *standard of care*, will rather broaden the scope of ethical attention (to the entire healthcare process) than decrease the level of protection of minors. However, if research is not considered to be an exceptionalist track in comparison to a validated standard of care, this has profound implications for the ethical assessment of research protocols, particularly with regard to the widely endorsed requirement to generate a direct benefit to the minor research subject concerned, and by extension also for the distinction between therapeutic and non-therapeutic research (cf. infra).

Protection versus trust

Minors are a vulnerable population and therefore deserve extensive protection. This protection, however, can be established in different ways. On the one hand, efforts can be made to shut minors off from what is deemed unethical. For example, research imposing significant risks to minors may be prohibited. Or, to guarantee a fully adequate protection of minors, the population can be excluded from clinical research altogether. However, this cannot be done without devastating drawbacks, since such an ethical stance is likely to block the access of minors to clinical research, denying them the benefits from medical progress.[8-10] The consequences of such a stance have become clear throughout recent history, and are tangible to date in the stringent lack of licensed drugs that are labeled for pediatric use.[1 2 4] On the other hand, minors can be protected by means of ethical safeguards that seek to deal with the drawbacks of medical progress without avoiding this drawbacks altogether. Doing so, the pursuit of medical progress can be balanced with the protection of minors.

When access and protection need to be balanced, however, trust will be essential. While at first glace, the act of trusting may seem naive to some, relationships of trust have great potential for negotiating the participation of a minor in a clinical trial (cf. chapter 4).[11] Nonetheless, relationships of trust also have important weaknesses, that should not be underestimated or ignored. Indeed, trust may increase the vulnerability of minors and their parents for deception, coercion, or harm.[12-15]

Given the devastating consequences of blocking the access of minors to clinical research, it is better to deal with drawbacks than to avoid them altogether. Therefore, the accurate protection of minors in clinical research should not lead to an overall skepticism or mistrust in research. Taking the drawbacks of trust seriously, however, criticism should be nurtured in minors and their parents, ethical expertise need to be created in clinicians, (sufficiently) independent sources of information should be provided to minors and their parents, and an adequate level of transparency should be guaranteed in research conduct.

Regulation versus discretion

Pediatric clinical research hosts a wide variety of research projects and research designs and brings together a large diversity of professional and lay actors, each with their own experience, values, skills, interests, personality, etc. By consequence, ethical issues and the way they are dealt with may vary substantially on a case-by-case basis. This research heterogeneity, however, is not addressed directly in the legal frameworks that govern pediatric clinical research in the EU.[16] Quite the reverse, important efforts have been made to harmonize European regulation, for the sake of encouraging and facilitating multicentre pediatric clinical research across the borders of EU member states.[17 18]

In this respect, the question whether a harmonized legal framework can adequately respond to the diverse specificities of individual cases is relevant. In the empirical observations made in this project, no indications were found that the legal framework proves hard to apply to specific situations. This is not surprising, since the general formulation of legal requirements leaves ample latitude to tailor their interpretation and implementation to the specificities of an individual case. Indeed, not everything in the law is arranged by law. Therefore, in principle, the legal framework appears to be adequate to deal with research heterogeneity. However, it is exactly the generality of legal requirements that also puts strong boundaries on their vigor. While nothing in the legal framework is redundant as such, nothing seems to be a true impetus for GCP either. In this respect, no indications that the European legal framework is inspiring for those committed to ethical issues on the interpersonal level were found this project.

Thus, while at the *institutional level*, a considerable urgency to deal with ethical issues exists (cf. chapter 9), at the *interpersonal level*, the realization of GCP-standards seems to depend largely on the individual qualities that the actors involved developed fortuitously. Since the individual patient only enters the scene at the impersonal level, omitting structural efforts to monitor and improve the quality of GCP at the interpersonal level is ethically negligent. Unfortunately, to date, no systematic mechanisms to monitor and improve the quality of GCP exist at the interpersonal level of trial conduct.

Informed consent versus documented consent

According to article 2(j) of the Clinical Trial Directive, informed consent is a "decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative […]".[17] To a considerable extent, this formulation has an administrative focus, requiring that consent be documented (as a written and dated document, signed by a competent person). Three elements, however, push informed consent beyond the administrative level: (1) decision making, (2) being informed, and (3) voluntariness.

Decision making

The definition in the Clinical Trial Directive states that informed consent is a decision. The outcome of the decision (the signature of a consent document), however, does not reveal much about what reasoning –if any- precedes the decisional outcome.

The observations of informed consent discussions in this project revealed no indications that -paradigmatically- informed consent is grounded in a well-considered and rational decision. In addition, several factors challenge the premise that written consent is preceded by a duly informed, well-considered, rational decision. First, the fact that informed consent is granted by competent persons does not imply that competences are actually used to take a stance towards a study protocol. Rationality is not necessarily the golden standard of all important decisions we make in life, and other factors (particularly tacit elements like hope, trust, or dependency) may shape decisions to grant informed consent. In this respect, one parent in our empirical study clearly stated to the researcher: "whatever you say is good for the child, we'll do it". Also other studies indicated several issues that work against rational decision making, such as inadequacies in understanding the research,[19-22] and emotional distress.[23]t One study even indicated that 10 out of 68 parents did not remember that they had signed up for a research protocol.[20] Second, several clinicians in our study suggested that granting informed consent is (nearly) customary, since (almost) all patients with the same disease are enrolled in a clinical trial. In this respect, consent appears as a customary commitment to the joint efforts of clinicians, parents and the minor to manage the disease in all available manners, rather than a commitment to a specific study protocol.

Although obviously, consent discussions can be well-considered and rational decisions, they might be *a priori decision*s as well, representing and confirming a positive stance towards research that parents already had before recruitment. This hypothesis of *a priori* decision-making would be consistent with three other observations in this project. First, two planned observations were canceled because the parents were considered to be too unlikely to consent. This suggests the researcher concerned traced an unfavorable *a priori* stance towards research. Second, most parents did not show any criticism towards research participation, for example by asking questions or discuss specific aspects of the study more thoroughly. In fact, only two parents, who clearly had a critical stance towards clinical research, accounted for nearly all the questions that parents formulated in our study. Also this critical stance is consistent with the idea of *a priori* decision-making. Third, we observed an overall willingness to grant informed consent. Also corridor chat with the clinicians in our study confirmed that refusal to participate in research was rather exceptional. Given the uncritical attitude of most parents, this willingness to consent might suggest a positive *a priori* stance towards research in general, rather than a duly informed endorsement of the study protocol.

Because several indications in our observations suggest that parents create little basis for making rational and well considered decisions, we suggest that the hypothesis of a priori decision making is to taken seriously and investigated further.

Being informed

Being informed is not the same as merely receiving information. It suggests a certain level of understanding. And understanding is not the same as memory. This, however, needs not to be a tragedy, since the major problems in the provision and understanding of information that have been reported in literature[20-22 24 25] need not necessarily to prevent, or even bother parents from making a determined decision on research participation.

From our observations, we have no indications that paradigmatically, parents were systematically provided with legally required (or other) information. Quite the reverse, the information provided varied significantly on a case-by-case basis. In addition, most parents clearly did not seek to get to the bottom of the research project and, as already has been pointed out, the parents in our study formulated remarkably few questions about the research.

Voluntariness

The potential for *a priori* and *customary* decision-making, makes that research participation is neither obligatory, nor unusual. In this regard, informed consent may rather be a decision not to drop out of certain practices that surround the minor in the hospital, than a decision to sign in into a research project. Against this background, however, voluntariness and the right to withdraw are of primordial importance. We have observed that this right was frequently emphasized, and we strongly suggest that researchers be extremely clear on the voluntariness of research participation, and the right to withdraw from the project at any time, without detriment to the minor.

Informed consent versus documented consent

On the one hand, informed consent presents itself as a formal permission to enroll a minor in the protocol, and can be regarded as *documented consent.* On the other hand, informed consent can be a duly informed and well-considered decision to enroll a minor in a clinical trial, and can be regarded as *informed consent*.

Documented consent and informed consent can be regarded the one ends of a broad spectrum. Where consent is currently situated in the spectrum, will vary from case to case. Where consent should be situated in this spectrum, is an important moral question that needs further normative reflection. Should we truly respect a family's culture of making poorly informed and ill-reflected decisions? Or should we nurture well-informed and ripe decision-making?

Assent versus compliant behavior

The difficulties in turning the procedure of granting consent into a truly informed and well-considered decision are also applicable to assent. Assent, the affirmative agreement of a minor to participate in a clinical trial, is not explicitly required by the Clinical Trial Directive. Nonetheless, the concept has been debated extensively in literature[25-33] and has been adopted in the guidelines on the implementation of the Directive provided by the EMA.[34]

In the consent discussions that were observed in this study, written assent was requested from the minor at several instances. All minors agreed to assent. From our observations, however, it is not clear whether this assent is grounded in a solid commitment to the trial, or in the compliant attitude that most minors in our study conveyed.

In contrast to the clear willingness to provide written assent, our observations also indicate that minors may lack interest and willingness to take part in decisions on research participation, even when their age and maturity enables them to do so. To our opinion, such disinterest or unwillingness to take part in the decision should be respected, and assent should not force minors to form an opinion on decisions they prefer to leave to someone else altogether.

Direct benefits versus valid research results

Since the benefit of clinical research is by nature contingent and the very purpose of clinical research is to find out whether additional benefit will be generated, speaking of benefit at the time of the consent discussion may be jumping to conclusions that still need to be drawn. In addition, also the fact that many trials eventually do not result in a direct therapeutic benefit for the subject should be recognized. Claiming a direct benefit to the individual patient as the outcome of a contingent scientific process yet to conduct therefore seems particularly imprudent. Reasons enough to be careful in discussing research benefits with parents and the practitioners in our empirical study of consent discussions seemed to be very much aware of that. In addition, the parents and minors in our study did not indicate that (direct) benefit was a prerequisite for research participation anywhere in our observations.

The mere fact that reliable predictions about benefit cannot be made, however, does not render the concept of benefit worthless. Obviously, when researchers conduct research, they pursue a benefit, be it rather in a process-oriented than a result-oriented fashion. Here, valid data seem to be the true benefit of research, rather than any direct benefit to the individual.[5] Nonetheless, the concept of direct benefit has earned a prominent place in medical ethics and health law, particularly as a counterweight to the risks involved in a clinical trial. In our opinion, however, direct benefit seems to be a very limited standard to assess the ethical acceptability of pediatric clinical research in comparison to valid results, as this standard enables to value both positive and negative research outcomes.

Nonetheless, direct benefit enjoys a prominent position in the assessment of research protocols by ethics committees. The standard is used to weigh the acceptability of risks, based on the rationale that the greater the potential benefit involved, the lower the risk threshold should be. For example, major legal regulation requires that basically, non-beneficial research does not exceed stringent minimal-risk and minimal-burden thresholds.[35 36] Also the Clinical Trial Directive requires proportionality between risks and benefits, as article 3,2(a) stipulated that “a clinical trial may be undertaken only if the

foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients."[17]

As has been demonstrated, however, in pediatric research the expected benefits do not provide a convincing ground to assess whether potential risks are justified in pediatric research for at least two reasons. First, in a setting with a share of off-license and off-label treatments as high in pediatrics, the risks characteristic to medical experimentation are never far away. While clinical trials are conducted in controlled conditions, off-license and off-label treatments entail medical experimentation in an uncontrolled fashion. Thus, in many instances, it might be advantageous to be in a trial compared to off-label treatments, at least for what is concerned the risks. Second, due to the contingent nature of benefits, predictions about expected (direct) benefits come at risk of being highly speculative.

In our observations of consent discussions, we found no discussion of risk-benefit ratios. In fact, hardly any explicit attention was paid to the (direct) benefits of research participation. Therefore, the risk to harm when not participating in the trial (*i.e.* the risks of the standard of care, of off-label or off-license treatment, or of non-treatment) may provide a better basis to assess the acceptability of the risks to harm that a trial entails.

Harmonization versus Diversification

Given the generally recognized priority to catch up with the development of drugs for use in the pediatric population, one would logically expect that the recently issued regulation rather simplifies the conduct of clinical research in minors than complicates it. Unfortunately, the reverse may be the case. While in the EU drugs are being licensed for the bulk of the 27 member states in one single marketing authorization procedure, the process leading to marketing authorization is much more diversified. The main cause of regulatory diversity is the coexistence of several regulatory frameworks, both at the supranational level and the level of individual EU Member states.[37 38] Due to this regulatory diversity, a number of contradictory provisions exist at the supranational level, and a considerable diversity of legal requirements must be complied with at the national level, dependent on where the research takes place. Obviously, it would be of clear interest to sponsors, researchers, and probably also research subjects and their parents if this diversity were reduced to the extent possible. Such reduction, however, should not work against the particular identity of individual member states. Nonetheless, it is questionable to what extent the current diversity of legal provisions actually serves the specific identity and needs of individual member states. Therefore, in my opinion, there is still a substantial potential for further harmonization.

In addition, the harmonization process should not be limited to harmonization of relevant legal provisions, but also cover the operational implementation of legal requirements. Particularly the work of ethics committees is open to further streamlining in this respect.[39]

The way forward

The seven ethical tensions that have been discussed in this general conclusion all challenge the current reflection on the ethical, legal, and social issues in pediatric clinical research. In addition, this discussion confronts clinical practice, medical ethics, and health law with many important and yet unanswered questions.

In the integrative approach of ethical, legal, and social issues that has been proposed in this dissertation it is neither the intention, nor the objective to address such questions by resolving them, for example by proposing clear-cut, ready to implement recommendations. Rather, this integrative approach suggests that adequate contextual analysis, normative qualification, and practical guidance will enable all parties involved to make better and more ethical decisions. In this way, medical ethicists or legislators do not pinch the pith of ethical decision-making, but leave it to those who are actually charged with these decisions in practice. At the same time, the integrative approach enables ethical reflection and legal analysis to make legitimate use of large scopes of data, methodologies, and ethical theories, regardless their problem-solving capacities with regard to specific cases. For sure, limiting ethical and legal reflection to problem solving would be a very reductionist approach to medical ethics and health law.

The discussion of seven ethical tensions in this general conclusion is thus not an endpoint of ethical and legal analysis, and the results of ethical and legal analysis are not function as an ethical oracle. Rather, they are a catalyst for ethical decision making, supporting those who are charged with the core decisions in pediatric clinical research conduct. To support ethical decision making, however, continuous enquiry of the ethical, legal, and social issues in pediatric research conduct will remain necessary, to adequately respond to new scientific evolutions and changing social contexts.

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Summary

Background

Although Harry Shirkey reported already in 1968 that in absence of pediatric clinical research minors would be turned into 'therapeutic orphans', pediatric patients have been ignored in clinical research for long, and systematic efforts to encourage the inclusion of minors in clinical studies only came decades later. Today, the urgent need for pediatric clinical research in the population of minors continues to exist, even though it has been generally recognized that pediatric clinical trials are indispensible to provide minors with an equitable gamut of safe and efficacious drugs as their adult counterparts.

Because of the important differences between adults and minors –both as *persons* and as *populations*- paradigms of clinical research, research ethics and research regulation that are grafted on the competent adult do not adequately respond to the specifics of pediatric clinical research. Therefore, specific attention must be paid to the ethical, legal, and social issues in pediatric clinical research. In other words: One size does not fit all.

Objectives

Four research objectives are central to this dissertation: the (1) enhancement of the access to and insight in the European legal frameworks that govern pediatric clinical research; (2) comparative analysis of relevant regulation at the supranational level and at the national level; (3) enquiry of the operational implementation of ethical and legal requirements in informed consent discussion in clinical research; and (4) ethical analysis of specific issues in pediatric clinical research.

Research results

In chapter 1, the European legal framework (supranational level) governing pediatric clinical trials is analyzed from the perspective of the major ethical concerns in pediatric research. The four principles of biomedical ethics are used as a conceptual framework (1) to map the ethical issues addressed in the European legal framework, (2) to study how these issues are commonly handled in competent adults, (3) to detect workability problems of these paradigmatic approaches in the specific setting of pediatric research, and (4) to illustrate the strong urge to differentiate, specify, or adjust these paradigmatic approaches to guarantee their successful operation in pediatric research. In addition, a concise comparative analysis of the European regulation is made. To conclude the analysis, our findings are discussed against the background of existing ethical discussions on issues specific to pediatric clinical research.

In chapter 2, the regulation of pediatric clinical research at the level of individual EU member states is mapped and analyzed. The analysis focuses on the way in which the

national and supranational legal frameworks address five ethical issues that are specific to pediatric clinical research: (a) informed consent, (b) the necessity to conduct research in minor subjects, (c) the interests of the subject concerned, (d) the risks and burdens involved, and (e) the pediatric expertise of protocol review committees. The chapter is concluded by a discussion of the harmonization and diversification of the legal requirements that govern pediatric clinical research in the EU.

Chapter 3 provides an overview of the requirements for involving minors in medical experiments in Belgium. In this chapter, the Law of 7 May 2004 concerning experiments on the human person (LEH) is analyzed, and dissimilarities between the LEH and the European Directive are discussed.

In chapter 4, it is analyzed how the enrollment of minors in clinical trials is negotiated within relationships of mutual trust between clinicians, minors, and their parents. After a brief description of the problems associated with involving minors in clinical research, it is considered how existing ‘‘relationships of trust’’ can be used as a place where the concerns of research subjects can be more fully discussed and addressed. Building on the tacit recognition of trust found in The European Clinical Trials Directive, policy recommendations for clearer, more ethically informed guidelines for enrolling minors in clinical research are made.

Chapter 5 explores seven bottlenecks in the ethical guidance and legal regulation that currently govern pediatric clinical research: (1) the integration of research in therapy, (2) the education of clinicians, (3) the empowerment of families, (4) the harmonization of protocol review, (5) the assessment of non-clinical research objectives, (6) the control of placebo use, and (7) the provision of fair incentives for pediatric research conduct. For all of these issues, a clear view on the way forward is largely lacking, either because these issues have not been discussed in depth to date, or because the existing debates have failed to generate a generally supported consensus.

In chapter 6, the ethical concerns in two potential tracks of seeking access to investigational medicinal products for minors are explored: access on an individual basis, or collective access via patient organizations. In the discourse, several unique ethical and regulatory concerns related to the direct negotiation of access to IMP for minor patients are identified, focusing on product safety, the recruitment of research subjects, the unnoticed entry of market mechanisms in the recruitment of research subjects, and the sidelining of third parties in the recruitment process.

Chapter 7 focuses on the pursuit of non-clinical research objectives in pediatric clinical research. While over the past decades important efforts have been made to regulate the involvement of children in clinical trials, current ethical and legal procedures surrounding clinical trials in minors (US/EU) are not designed to consider and assess the non-clinical use of medical technologies such as fMRI. Nonetheless, non-clinical applications of pediatric fMRI cannot be developed without conducting clinical trials in children. In this chapter,

diverse ethical issues related to the non-clinical applications of fMRI are discussed from the perspective of pediatric clinical trial regulation.

In chapter 8, major ethical issues in the development and supply of orphan drugs are discussed. This chapter focuses on addressing the commercial disinterest in developing drugs for rare conditions. While several interventions have been made in the regulatory field, existing regulations leave the overarching question on the righteous place of orphan drugs in resource allocation systems unanswered. In this chapter, major ethical issues in the development and supply of treatments for rare conditions are analyzed. Subsequently, an ethical framework is proposed, aiming at helping health policy makers in moving forward in the difficult issue of justly allocating resources to the prevention and treatment of rare diseases.

In chapter 9, it is explored how the legal framework governing pediatric clinical research is implemented in informed consent discussions. In this chapter, the results of an observational study of informed consent discussions are discussed.

Conclusion

In this dissertation, the ethical, legal and social aspects of clinical research in the EU have been investigated from a multidisciplinary perspective. In the first four chapters, the access to and insight in the European legal frameworks that govern pediatric clinical research has been increased, by mapping and analyzing national and supranational legislation. The analysis of legal requirements in chapters 1-3 also covers a comparative analysis of relevant regulation at the supranational level and at the national level. Specific attention has been paid to the Belgian situation. In addition, the regulation of trust in the European legal framework surrounding pediatric clinical research has been analyzed, as an illustration of the tacit elements that are essential to the operational implementation of legal requirements.

Chapters 5-8 have focused on the ethical analysis of specific issues in pediatric clinical research, including (1) the integration of research in therapy, (2) the education of clinicians, (3) the empowerment of families, (4) the harmonization of protocol review, (5) the assessment of non-clinical research objectives, (6) placebo use, (7) the provision of fair incentives for pediatric research conduct, (8) access to investigational medicinal products, and (9) the development and supply of orphan drugs.

An enquiry of the operational implementation of ethical and legal requirements in informed consent discussion has been presented in chapter 9.

To conclude the analysis in this dissertation, seven controversies in contemporary pediatric clinical research are discussed: (1) standard of care versus state of the art disease management, (2) protection versus trust, (3) regulation versus discretion, (4) harmonization versus heterogeneity, (5) informed consent versus documented consent, (6) assent versus procedure compliance, and (7) direct benefit versus valid research results.

Samenvatting

Probleemschets

Hoewel Harry Shirkey reeds in 1968 opmerkte dat minderjarigen bij gebrek aan klinische proeven "therapeutische wezen" zouden worden, werden kinderen tot voor kort sterk genegeerd in het klinisch onderzoek. Systematische inspanningen om klinisch onderzoek bij minderjarigen aan te moedigen, kwamen zelfs pas decennia later.

Vandaag de dag bestaat deze nood aan klinisch onderzoek bij minderjarigen onverminderd voort, ook al wordt de nood om minderjarigen in klinische proeven te includeren nu algemeen erkend.

Omwille van de significante verschillen tussen kinderen en volwassenen (zowel op het niveau van het individu als op het niveau van de populatie) kunnen de paradigmata van wetenschappelijk onderzoek, medische ethiek en gezondheidsrecht die gebruikt worden voor de regulering van klinische proeven met competente volwassenen, niet zonder meer voor de regeling van klinische proeven met kinderen worden ingezet. Daarom moet specifieke aandacht besteed worden aan de ethische, juridische en sociale aspecten van klinische proeven met minderjarige proefpersonen. Met andere woorden: "one size doesn't fit all".

Doelstellingen

Centraal in deze dissertatie staan de volgende vier doelstellingen: (1) de toegang tot de regelgeving die klinische proeven met kinderen in Europa regelt verbeteren, en het inzicht erin vergroten; (2) een rechtsvergelijkende analyse van supranationale (Europese) en nationale regelgeving die van toepassing is op klinisch onderzoek met minderjarigen opstellen ; (3) de implementering van wettelijke vereisten inzake goede klinische praktijk onderzoeken; en (4) specifieke ethische kwesties met betrekking tot klinisch onderzoek met minderjarige proefpersonen analyseren.

Resultaten

In het eerste hoofdstuk wordt het Europese regelgevende kader dat klinische proeven met minderjarigen regelt kritisch beschouwd tegen de achtergrond van vier centrale ethische bekommernissen. De vier principes van biomedische ethiek worden in dit hoofdstuk gebruikt als conceptueel kader om (1) ethische kwesties in het regelgevend kader in kaart te brengen, (2) te bestuderen hoe deze kwesties worden aangepakt in de sturing van klinische proeven met competente volwassenen, (3) de problemen die deze paradigmatische aanpak vertoont in de specifieke context van onderzoek met kinderen te detecteren en (4) de drang om bestaande paradigmata toch te doen functioneren voor klinisch onderzoek bij kinderen (bv. door differentiatie, specificatie, of aanpassing) te illustreren.

In hoofdstuk twee wordt de regelgeving waaraan klinische proeven bij minderjarigen in de verschillende Europese lidstaten moet voldoen in kaart gebracht en geanalyseerd. In dit hoofdstuk wordt de regeling van vijf ethische kwesties die specifiek zijn voor onderzoek met minderjarigen onderzocht: (1) geïnformeerde toestemming, (2) de noodzaak om het onderzoek te verrichten bij minderjarigen, (3) de belangen van de betrokken minderjarigen, (4) de risico's en belastingen die eigen zijn aan het onderzoek, en (5) de specifieke expertise van ethische commissies inzake het betrekken van minderjarigen in klinisch onderzoek. Het hoofdstuk eindigt met een kritische beschouwing van de harmonisering en diversificatie van wettelijke vereisten die binnen de EU gelden.

In het derde hoofdstuk worden de wettelijke vereisten voor klinisch onderzoek met minderjarigen in België in kaart gebracht. In dit hoofdstuk wordt de wet van 7 mei 2004 inzake experimenten op de menselijke persoon besproken, met bijzondere aandacht voor de punten van verschil tussen deze wet en de Europese Richtlijn met betrekking tot klinische proeven.

In het vierde hoofdstuk wordt onderzocht hoe de deelname van minderjarigen aan klinische proeven wordt besproken binnen de vertrouwensrelaties tussen artsen, minderjarigen en hun ouders. In dit hoofdstuk wordt bekeken hoe bestaande vertrouwensrelaties aangewend kunnen worden om de specifieke belangen van minderjarige proefpersonen te bespreken en behartigen. Vertrekkende vanuit de impliciete erkenning van het belang van de vertrouwensrelatie in de Europese wetgeving die klinische proeven met minderjarigen regelt, worden aanbevelingen voor de rekrutering van minderjarigen voor klinisch onderzoek geformuleerd.

In hoofdstuk vijf worden zeven actuele knelpunten in het hedendaagse klinisch onderzoek met minderjarigen besproken: (1) de integratie van onderzoek in de therapeutische praktijk, (2) de ethische vorming van clinici, (3) de emancipatie van families, (4) het stroomlijnen van de ethische evaluatie van onderzoeksprotocols, (5) de evaluatie van niet-klinische onderzoeksdoelstellingen, (6) gecontroleerd placebo gebruik en (7) het voorzien van rechtvaardige financiële stimuli. De ethische reflectie inzake deze zeven kwesties is van bijzonder belang, omdat er geen consensus bestaat over hoe ze aangepakt moeten worden, of omdat ze tot op heden onvoldoende onderzocht werden.

In het zesde hoofdstuk worden de ethische kwesties met betrekking tot de toegankelijkheid van experimentele geneesmiddelen onderzocht, zowel in het geval dat individuen experimentele geneesmiddelen proberen te bekomen, als in het geval dat patiëntenverenigingen voor het collectief van hun leden toegang tot experimentele geneesmiddelen zouden zoeken. Hierbij worden specifieke ethische en regelgevende kwesties in kaart gebracht, met bijzondere aandacht voor (1) productveiligheid, (2) de rekrutering van proefpersonen, (3) de vermarkting van deelname aan klinisch onderzoek, en (4) het uitsluiten van externe partijen in het rekruteringsproces.

In het zevende hoofdstuk wordt de problematiek van niet-klinische onderzoeksdoelstellingen beschouwd. Ondanks het feit dat de voorbije decennia werd

geïnvesteerd in de regeling van klinisch onderzoek met kinderen, ontsnappen bepaalde types van onderzoek –zoals klinisch onderzoek met niet-klinische doelstellingen- aan daadwerkelijke ethische evaluatie van de inherente risico's voor het kind en de samenleving. In dit hoofdstuk worden daarom verscheidene ethische kwesties met betrekking tot klinische proeven met niet-klinische doelstellingen in kaart gebracht en geanalyseerd.

In het achtste hoofdstuk worden de ethische kwesties in de ontwikkeling en verstrekking van medicijnen voor zeldzame ziektes geanalyseerd. In dit hoofdstuk wordt nagegaan hoe kan worden omgegaan met het gebrek aan commerciële interesse in de ontwikkeling van medicijnen voor zeldzame ziekten, vanuit de vraag naar de rechtmatige plaats van weesgeneesmiddelen in de publieke gezondheidszorg.

In het negende hoofdstuk wordt in kaart gebracht hoe de geldende regelgeving met betrekking tot goede klinische praktijk wordt geïmplementeerd in oudergesprekken waarin de deelname van minderjarigen aan klinische proeven wordt besproken.

Besluit

In deze dissertatie werden de ethische, juridische en sociale kwesties in klinisch onderzoek met minderjarigen in de Europese Unie onderzocht vanuit een multidisciplinair perspectief. De eerste vier hoofdstukken creëerden toegang tot en inzicht in de bestaande regelgeving, door de geldende wetten in kaart te brengen en te analyseren. Daarnaast omvatten hoofdstuk 1-3 ook een rechtsvergelijkende analyse. Bijzondere aandacht werd besteed aan de Belgische regelgeving. Tot slot werd ook het belang van vertrouwensrelaties voor de succesvolle implementering van wettelijke vereisten geanalyseerd.

In het vijfde tot en met achtste hoofdstuk werden specifieke ethische kwesties in het klinisch onderzoek met minderjarige proefpersonen belicht, waaronder (1) de integratie van onderzoek in de therapeutische praktijk, (2) de ethische vorming van clinici, (3) de emancipatie van families, (4) het stroomlijnen van de ethische evaluatie van onderzoeksprotocols, (5) de evaluatie van niet-klinische onderzoeksdoelstellingen, (6) gecontroleerd placebo gebruik, (7) het voorzien van rechtvaardige financiële stimuli, (8) de toegankelijkheid van experimentele geneesmiddelen, en (9) de omgang met weesgeneesmiddelen voor zeldzame ziekten.

In het negende hoofdstuk werden de resultaten van ons observationeel onderzoek naar de implementering van wettelijke vereisten tijdens oudergesprekken betreffende de deelname van een minderjarige proefpersoon aan een klinische proef voorgesteld.

Tot slot werden zeven ethische spanningen in het hedendaagse klinisch onderzoek met minderjarigen belicht: (1) standaardtherapie versus vernieuwende aanpak, (2) bescherming versus vertrouwen, (3) regelgeving versus oordeelkunde, (4) harmonisatie versus diversiteit, (5) geïnformeerde toestemming versus gedocumenteerde toestemming, (6) geïnformeerde instemming versus medewerking en (7) therapeutisch voordeel versus kwaliteitsvolle resultaten.

Curriculum Vitae

Wim Pinxten (°1977) has a background in religious studies (MA), law (BA), and applied ethics (MA). In 2006, he joined the Interfaculty Centre for Biomedical Ethics and Law of the KULeuven as a PhD student, enquiring the ethical, legal, and social aspects of pediatric clinical research.

As a researcher in medical ethics and health law, he has been involved in several EC-funded projects at the International Forum for Biophilosophy and the Katholieke Universiteit Leuven.

His research interests are in the ethical, legal and social aspects of clinical research in (minor) human subjects, ageing and senescence, new medical technologies, genomics research, global justice in healthcare, and rare diseases and orphan drugs.

In 2010 he joined the Department of Medical Ethics and Philosophy of Medicine of the ErasmusMC as a postdoctoral researcher. In addition, he is part-time lector in ethics at the Katholieke Hogeschool Leuven.

List of Publications

Pinxten, W., Nys, H., Dierickx, K. (2010). Frontline ethical issues in pediatric clinical research. Ethical and regulatory aspects of seven current bottlenecks in pediatric clinical research. European Journal of Pediatrics European Journal of Pedatrics 169(12),1541-8.

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